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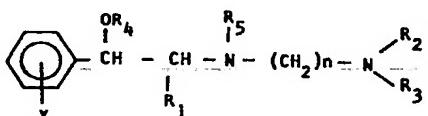
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(54) Amino-alcohol derivatives and processes for their preparation.

(57) Amino-alcohol derivatives of the formula,



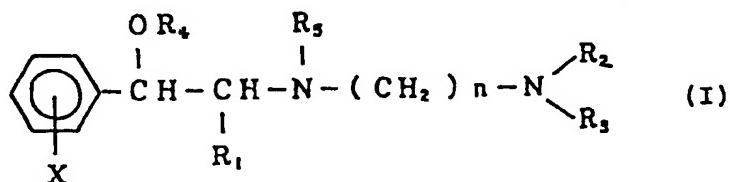
thereof, are effectively useful as medicines and agricultural chemicals. Processes are also disclosed for preparing such compounds.

where R<sub>1</sub> is a straight or branched alkyl group having 3 to 8 carbon atoms, R<sub>2</sub> and R<sub>3</sub> are each a lower alkyl group, or R<sub>2</sub> and R<sub>3</sub> form a 5- to 7-membered ring together with the adjacent nitrogen atom which may have an oxygen atom attached thereto, R<sub>4</sub> is a hydrogen atom or a lower alkyl group, R<sub>5</sub> is a hydrogen atom or a lower alkyl group, X is a hydrogen or halogen atom or a lower alkyl or lower alkoxy group, and n is an integer of 2 or 3, and acid addition salts

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"AMINO-ALCOHOL DERIVATIVES AND PROCESSES FOR  
THEIR PREPARATION"

This invention relates to novel amino-alcohol derivatives and more particularly to amino-alcohol derivatives of the formula (I),



where  $\text{R}_1$  is a straight or branched alkyl group having 3 to 8 carbon atoms,  $\text{R}_2$  and  $\text{R}_3$  are each a lower alkyl group, or  $\text{R}_2$  and  $\text{R}_3$  form a 5- to 7-membered ring together with the adjacent nitrogen atom which may have an oxygen atom attached thereto,  $\text{R}_4$  is a hydrogen atom or a lower alkyl group,  $\text{R}_5$  is a hydrogen atom or a lower alkyl group,  $\text{X}$  is a hydrogen or halogen atom or a lower alkyl or lower alkoxy group, and  $n$  is an integer of 2 or 3, or acid addition salts thereof. The invention further relates to processes for preparing these compounds.

As has been strongly suggested in the art, glutamic acid acts as an excitatory neurotransmitter at the central nervous systems of higher animals and at the neuromuscular junctions of lower animals ["Glutamate as a Neuro-transmitter" edited by G. D. Chiara & G. L. Gessa: Raven

Press, New York, 1981 and H. M. Gerschenfeld: *Physiol. Rev.*, 53, 1-119 (1973)]. It has also been reported that dystropy, rigidity, tremors, convulsions and the like are induced by the administration of kainic acid, domoic acid, quisqualic acid, ibotenic acid or the like, which acids are extremely strong agonists for glutamic acid in higher animals [Oleny et al.: *Brain Res.*, 77, 507-512 (1974)].

It is known that as ageing proceeds, the central and peripheral nervous systems would undergo hypoergia to 10 develop Parkinson's disease, motoneuron disorders, dementia, tremors, spinocerebellar degeneracy and the like. These diseases are considered to be attributable to off-balanced equilibration between excitatory nerves and inhibitory nerves (for example, the equilibration between 15 glutamic acid and GABA) due to loss of neurons at certain specific sites or overall hypoergia of the nervous systems [Toshishige Hirai: *Shinkei Shimpo*, 17, 69 (1973)].

With the foregoing in view, medicines that can selectively block glutamic acid are useful for the therapy 20 of neuropathy from which the senile would most often suffer and which would involve such complaints as vertigo, shoulder discomfort, convulsions, tremors and the like, all of them resulting from off-balanced nervous systems or hyperstenia in muscle discharge.

25 Glutamic acid also acts as an excitatory neurotransmitter for neuromuscular junctions of insects. Chemicals capable of blocking glutamic acid are therefore

suitable for agricultural use for their ability to reduce and weaken insects' activities [Morifusa Eto: Kagaku to Seibutsu, 21, 725 (1983)].

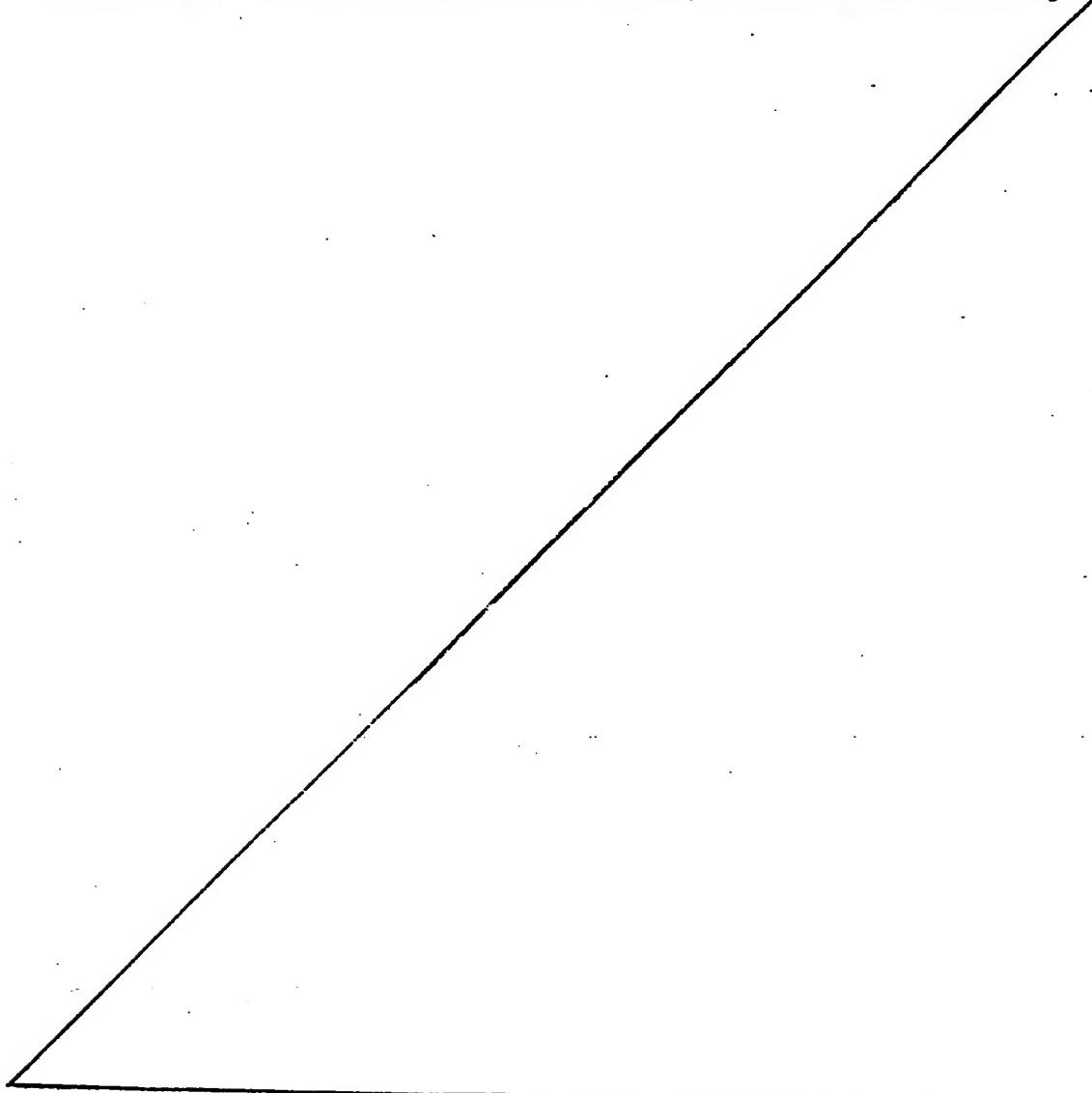
It has now been found that amino-alcohol derivatives 5 of the formula (I) above have excellent blocking effects against glutamic acid as well as neuraxial muscle relaxing effects, i.e. rigidity reducing and releasing effects on anemic decerebrate rigidity samples.

This result suggests that the inventive compounds 10 are useful for the therapy of a complaint which would have spastic paralysis and rigidity and these compounds are expected to suppress or release dyskinasis, athetosis, myoclonus, tic, tremors, dystonia and ballismus of neuropathy.

15 Some compounds are known which are structurally similar to the compounds contemplated by the present invention. Such known compounds are 2-(2-dimethylaminoethylamino)-1-phenylpropan-1-ol [Sv. Zikolova and L. Zhelyazkov: Tr. Nauchno-Izsled. Inst. Farm., 3, 14-19 20 (1961) (CA, 61, 9485b)], 1-phenyl-2-(2-piperidinoethyl-amino)propan-1-ol and 1-phenyl-2-(2-pyrrolidinoethylamino)-propan-1-ol [ibid., L. Zhelyazkov, A. Georgiev, Sv. Zikolova, P. Manolov, L Daleva and M. Kazandzhiev: Tr. Nauchnoizsled. Khim.-Farm. Inst., 1972, 7, 33-53 (CA, 79, 25 27099g) and L. Daleva, P. Manolov: Tr. Nauchnoizsled. Khim.-Farm. Inst., 1972, 7, 229-240 (CA, 79, 27213g)] and 2-(2-morpholinoethyl- amino)-1-phenylpropan-1-ol [Sv.

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Zikolova and L. Zhelyazkov: Farmatsiya, 14, (5), 16-21  
(1964) (CA, 62, 13135g)]. These prior art publications  
however are silent as to whether the known compounds would  
have blocking effects against glutamic acid. Experiments  
5 conducted by the present inventors show that those  
compounds are only marginal in their glutamic acid blocking.



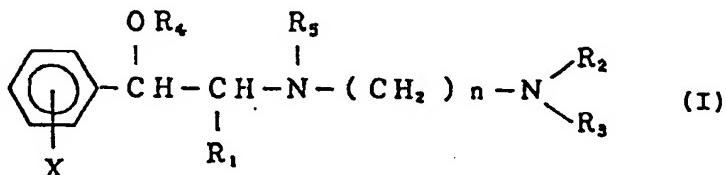
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effects and in their rigidity reducing and releasing effects as compared with the compounds of the invention.

It is an object of the present invention to provide novel amino-alcohol derivatives of the formula (I) above which have excellent blocking effects against glutamic acid and rigidity reducing and releasing effects and hence are effectively useful as medicines and agricultural chemicals.

Another object of the invention is to provide processes for preparing such compounds.

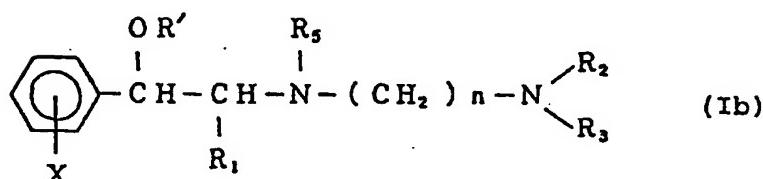
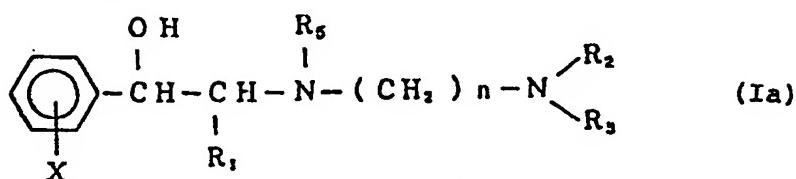
10 These and other objects and features of the invention can be attained by the provision of an amino-alcohol derivative of the formula (I),



where R<sub>1</sub> is a straight or branched alkyl group having 3 to 8 carbon atoms, R<sub>2</sub> and R<sub>3</sub> are each a lower alkyl group, or 15 R<sub>2</sub> and R<sub>3</sub> form a 5- to 7-membered ring together with the adjacent nitrogen atom which may have an oxygen atom attached thereto, R<sub>4</sub> is a hydrogen atom or a lower alkyl group, R<sub>5</sub> is a hydrogen atom or a lower alkyl group, X is a hydrogen or halogen atom or a lower alkyl or lower alkoxy group, n is an integer of 2 or 3, or an acid addition salt

thereof.

Amino-alcohol derivatives of the present invention contain two types of compounds, i.e. a compound of the formula (Ia) and a compound of the formula (Ib),

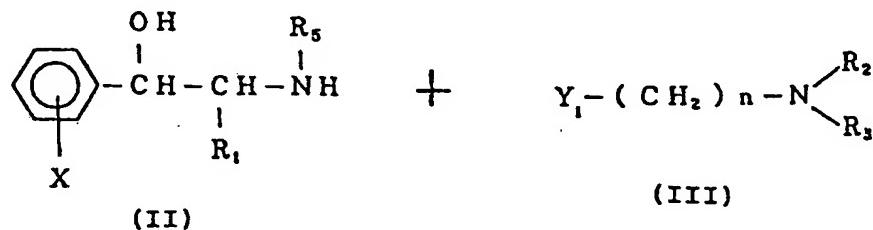


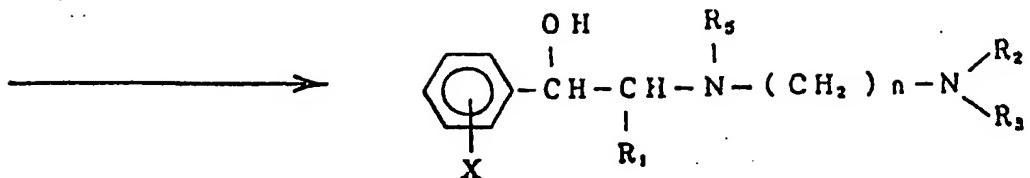
5 where R' is a lower alkyl group, and R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, X and n are as defined previously.

Both of these compounds of the invention can be prepared, for example, by one of the following processes.

Process 1

- 10 In accordance with the following reaction scheme, a compound of the formula (II) is reacted with a compound of the formula (III) to prepare the desired compound (Ia),





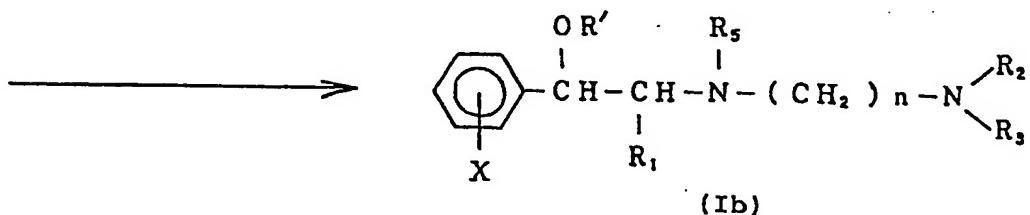
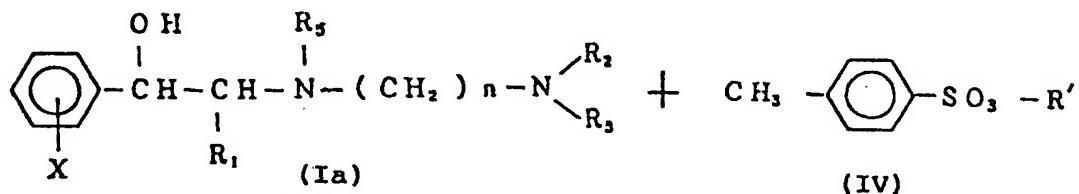
(Ia)

where  $\text{Y}_1$  is a halogen atom or a tosyloxy group, and  $\text{R}_1$ ,  $\text{R}_2$ ,  $\text{R}_3$ ,  $\text{R}_5$ ,  $\text{X}$  and  $n$  are as defined previously.

The reaction of the compound (II) with the compound (III) is effected at 50 to 150°C. This reaction may be conducted without a solvent under normal conditions, but it is possible to use an inert solvent.

#### Process 2

In accordance with the following reaction scheme, the compound (Ia) is reacted with a compound of the formula (IV) to prepare the desired compound (Ib),



where  $\text{R}'$  is a lower alkyl group, and  $\text{R}_1$ ,  $\text{R}_2$ ,  $\text{R}_3$ ,  $\text{R}_5$ ,  $\text{X}$  and  $n$  are as defined previously.

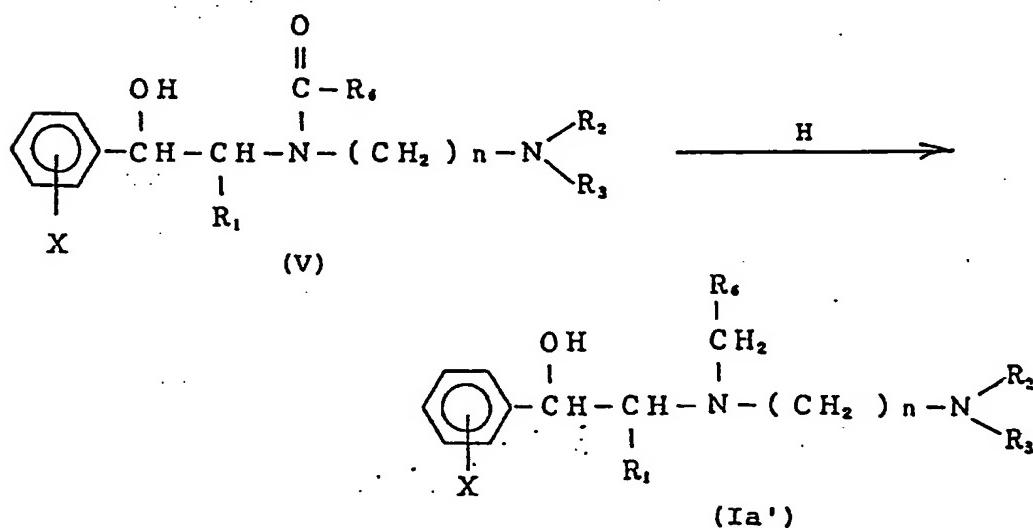
This reaction is conducted by reacting an alcoholate

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anion of the compound (Ia) with the compound (IV). The alcoholeate is obtained by treating the compound (Ia) with a base such as sodium hydride in an organic solvent such as benzene or toluene at room temperature to 150°C.

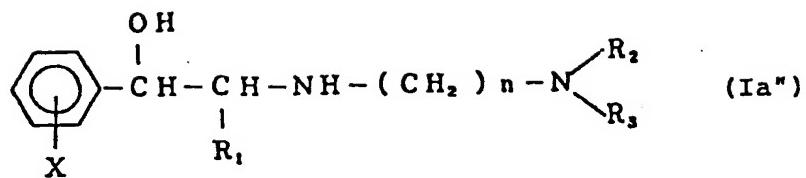
### 5 Process 3

In accordance with the following reaction scheme, a desired compound of the formula (Ia') is obtained by reducing a compound of the formula (V),



where  $R_6$  is a hydrogen atom or a lower alkyl group, and  $R_1$ ,  $R_2$ ,  $R_3$ ,  $X$  and  $n$  are as defined previously.

The compound (V) which is a starting material for this reaction is obtained by acylating a compound of the formula (Ia''),

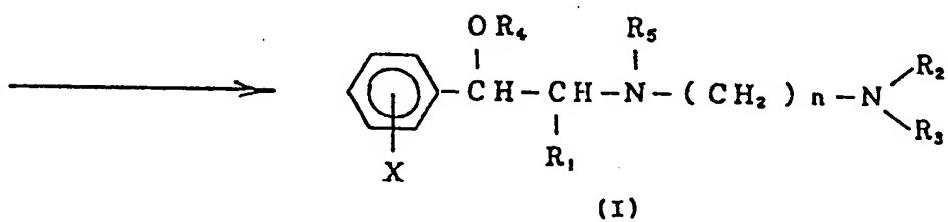
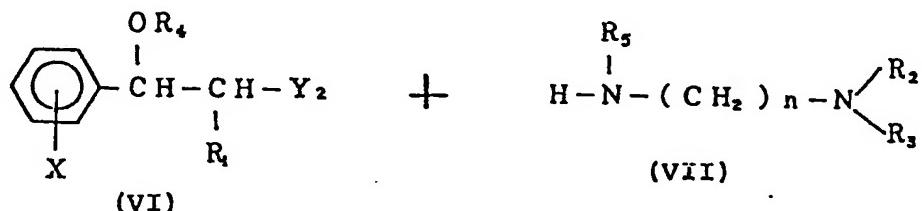


where  $R_1$ ,  $R_2$ ,  $R_3$ ,  $X$  and  $n$  are as defined previously.

The reaction is effected with use of a reducing agent such as lithium aluminum hydride in a solvent such as tetrahydrofuran or ether at 0°C to the boiling point of the solvent.

#### Process 4

In accordance with the following reaction scheme, a compound of the formula (VI) is reacted with a compound of the formula (VII) to prepare a desired compound of the formula (I),



where  $\text{Y}_2$  is a halogen atom, and  $R_1, R_2, R_3, R_4, R_5, X$  and  $n$

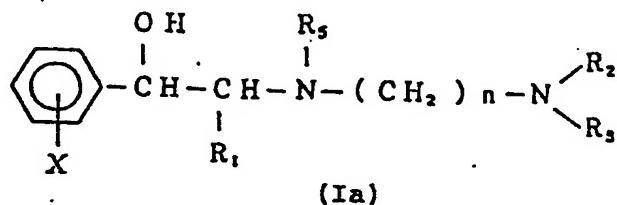
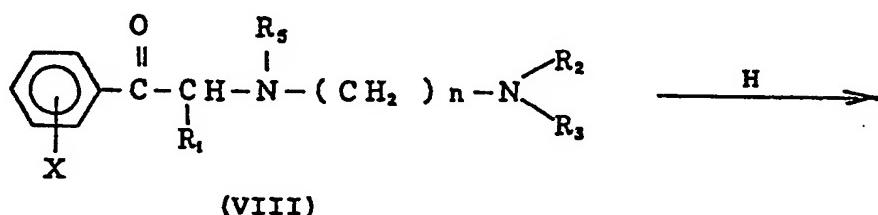
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are as defined previously.

The reaction of the compound (VI) with the compound (VII) is effected with or without a solvent at 50 to 150°C for 1 to 10 hours.

5 Process 5

In accordance with the following reaction scheme, the desired compound (Ia) is obtained by reducing a compound of the formula (VIII),



where  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_5$ ,  $X$  and  $n$  are as defined previously.

10 The reduction is effected in the usual manner. For example, the following reaction techniques may be employed.

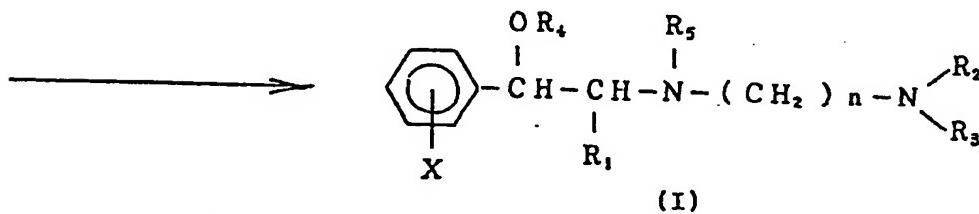
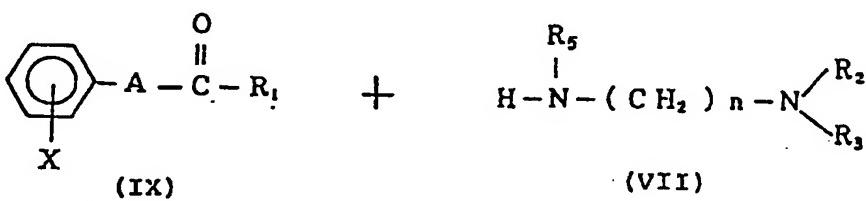
1) Hydrogenation in the presence of a catalyst such as Raney-nickel, platinum, palladium-carbon or the like in a solvent such as methanol or ethanol

15 2) Reduction using a metal hydride complex, for example, sodium borohydride in a solvent such as methanol or ethanol, or lithium aluminum hydride in an organic solvent such as ether or tetrahydrofuran

3) Reduction using an aluminum alkoxide such as aluminum isopropoxide in an organic solvent such as isopropanol or the like

Process 6

5 In accordance with the following reaction scheme, the desired compound (I) is obtained by reacting a compound of the formula (IX) with the compound (VII) under reducing conditions,



where A is  $\text{-C=}$  or  $\text{-CH-}$ , and  $\text{R}_1, \text{R}_2, \text{R}_3, \text{R}_4, \text{R}_5, \text{X}$  and  $n$  are 10 as defined previously.

In the case where A is  $\text{-C=}$ , the reaction is effected in the presence of zinc and sulfuric acid in a solvent such as methanol or ethanol at 50 to 150°C

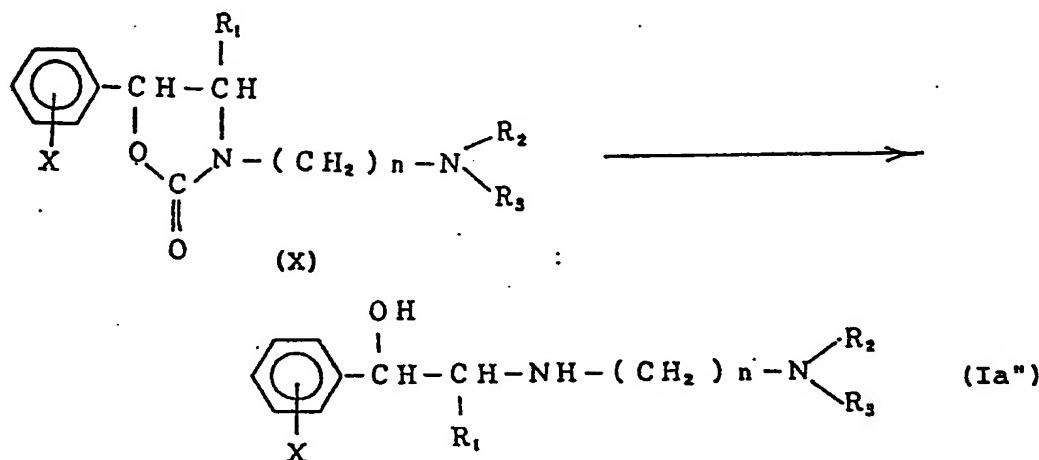
for 0.5 to 5 hours. In the case where A is  $\text{-CH-}$ , the 15 reaction is effected by hydrogenation in the

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presence of a catalyst such as Raney-nickel, platinum, palladium-carbon or the like in a solvent such as methanol or ethanol, or by reduction using a metal hydride complex, for example, sodium cyanoborohydride in a solvent such as 5 methanol or ethanol, preferably in a pH range of 6 to 9, or sodium borohydride in the presence of acetic acid and sodium acetate in a solvent such as alcohol-containing water.

Process 7

- 10 In accordance with the following reaction scheme, a desired compound of the formula (Ia") is obtained by hydrolyzing a compound of the formula (X),



where  $\text{R}_1$ ,  $\text{R}_2$ ,  $\text{R}_3$ ,  $\text{X}$  and  $n$  are as defined previously.

- This reaction is effected by hydrolyzing the compound 15 (X) in the presence of a base such as sodium hydroxide in alcohol-containing water at 50 to 100°C.

The amino-alcohol derivatives (I) thus prepared can be converted in conventional manner to their acid addition

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salts. Acid addition salts useful in the invention include, for example, hydrochlorides, hydrobromides, phosphates, sulfates, p-toluene-sulfonates, fumarates, citrates, maleates; tartrates and the like.

5 Each of the compounds contemplated by the present invention includes its stereoisomers, i.e. an erythro form (1RS,2SR) and a threo form (1RS,2RS), and its optical isomers (1R,2S), (1S,2R), (1R,2R) and (1S,2S). It is to be noted that these two types of isomers are within the scope  
10 of the invention.

The following compounds are particularly typical of the compounds (I) of the present invention.

Compound 1 : (1RS,2SR)-1-phenyl-2-(3-piperidinopropylamino)-  
pentan-1-ol dihydrochloride

15 Compound 2 : (1RS,2RS)-1-phenyl-2-(3-piperidinopropylamino)-  
pentan-1-ol dihydrochloride

Compound 3 : (1RS,2SR)-1-phenyl-2-(3-piperidinopropylamino)-  
hexan-1-ol dihydrochloride

Compound 4 : (1RS,2RS)-1-phenyl-2-(3-piperidinopropylamino)-  
20 hexan-1-ol dihydrochloride

Compound 5 : (1RS,2SR)-1-phenyl-2-(3-piperidinopropylamino)-  
heptan-1-ol dihydrochloride

Compound 6 : (1RS,2RS)-1-phenyl-2-(3-piperidinopropylamino)-  
heptan-1-ol dihydrochloride

25 Compound 7 : (1RS,2SR)-1-phenyl-2-(3-piperidinopropylamino)-  
octan-1-ol dihydrochloride

Compound 8 : (1RS,2RS)-1-phenyl-2-(3-piperidinopropylamino)-

octan-1-ol dihydrochloride

Compound 9: (1RS,2SR)-1-phenyl-2-(3-piperidinopropylamino)-  
nonan-1-ol dihydrochloride

Compound 10: (1RS,2RS)-1-phenyl-2-(3-piperidinopropylamino)-  
5 nonan-1-ol dihydrochloride

Compound 11: (1RS,2SR)-1-phenyl-2-(3-piperidinopropylamino)-  
decan-1-ol dihydrochloride

Compound 12: (1RS,2RS)-1-phenyl-2-(3-piperidinopropylamino)-  
decan-1-ol dihydrochloride

10 Compound 13: (1RS,2SR)-3-methyl-1-phenyl-2-(3-piperidino-  
propylamino)butan-1-ol dihydrochloride

Compound 14: (1RS,2RS)-3-methyl-1-phenyl-2-(3-piperidino-  
propylamino)butan-1-ol dihydrochloride

Compound 15: (1RS,2SR)-4-methyl-1-phenyl-2-(3-piperidino-  
15 propylamino)pentan-1-ol dihydrochloride

Compound 16: (1RS,2RS)-4-methyl-1-phenyl-2-(3-piperidino-  
propylamino)pentan-1-ol dihydrochloride

Compound 17: (1R,2S)-4-methyl-1-phenyl-2-(3-piperidino-  
propylamino)pentan-1-ol dihydrochloride

20 Compound 18: (1S,2R)-4-methyl-1-phenyl-2-(3-piperidino-  
propylamino)pentan-1-ol dihydrochloride

Compound 19: (1S,2S)-4-methyl-1-phenyl-2-(3-piperidino-  
propylamino)pentan-1-ol dihydrochloride

Compound 20: (1R,2R)-4-methyl-1-phenyl-2-(3-piperidino-  
25 propylamino)pentan-1-ol dihydrochloride

Compound 21: (1RS,2SR)-5-methyl-1-phenyl-2-(3-piperidino-  
propylamino)hexan-1-ol dihydrochloride

- Compound 22: (1RS,2RS)-5-methyl-1-phenyl-2-(3-piperidino-propylamino)hexan-1-ol dihydrochloride
- Compound 23: (1RS,2SR)-4-methyl-1-phenyl-2-(3-pyrrolidino-propylamino)pentan-1-ol dihydrochloride
- 5 Compound 24: (1RS,2RS)-4-methyl-1-phenyl-2-(3-pyrrolidino-propylamino)pentan-1-ol dihydrochloride
- Compound 25: (1RS,2SR)-4-methyl-2-(3-morpholinopropyl-amino)-1-phenylpentan-1-ol dihydrochloride
- 10 Compound 26: (1RS,2RS)-4-methyl-2-(3-morpholinopropyl-amino)-1-phenylpentan-1-ol dihydrochloride
- Compound 27: (1RS,2SR)-2-(3-dimethylaminopropylamino)-4-methyl-1-phenylpentan-1-ol dihydrochloride
- Compound 28: (1RS,2RS)-2-(3-dimethylaminopropylamino)-4-methyl-1-phenylpentan-1-ol dihydrochloride
- 15 Compound 29: (1RS,2SR)-4-methyl-1-phenyl-2-(2-piperidino-ethylamino)pentan-1-ol dihydrochloride
- Compound 30: (1RS,2RS)-4-methyl-1-phenyl-2-(2-piperidino-ethylamino)pentan-1-ol dihydrochloride
- 20 Compound 31: (1RS,2SR)-4-methyl-1-phenyl-2-(2-pyrrolidino-ethylamino)pentan-1-ol dihydrochloride
- Compound 32: (1RS,2RS)-4-methyl-1-phenyl-2-(2-pyrrolidino-ethylamino)pentan-1-ol dihydrochloride
- 25 Compound 33: (1RS,2SR)-4-methyl-2-[3-(perhydroazepin-1-yl)-propylamino]-1-phenylpentan-1-ol dihydrochloride
- Compound 34: (1RS,2RS)-4-methyl-2-[3-(perhydroazepin-1-yl)-propylamino]-1-phenylpentan-1-ol dihydro-

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- Compound 35: (1RS,2SR)-5-methyl-1-phenyl-2-(3-pyrrolidino-propylamino)hexan-1-ol dihydrochloride
- Compound 36: (1RS,2RS)-5-methyl-1-phenyl-2-(3-pyrrolidino-propylamino)hexan-1-ol dihydrochloride
- Compound 37: (1RS,2SR)-5-methyl-2-(3-morpholinopropyl-amino)-1-phenylhexan-1-ol dihydrochloride
- Compound 38: (1RS,2RS)-5-methyl-2-(3-morpholinopropyl-amino)-1-phenylhexan-1-ol dihydrochloride
- Compound 39: (1RS,2SR)-2-(3-dimethylaminopropylamino)-5-methyl-1-phenylhexan-1-ol dihydrochloride
- Compound 40: (1RS,2RS)-2-(3-dimethylaminopropylamino)-5-methyl-1-phenylhexan-1-ol dihydrochloride
- Compound 41: (1RS,2SR)-5-methyl-1-phenyl-2-(2-piperidino-ethylamino)hexan-1-ol dihydrochloride
- Compound 42: (1RS,2RS)-5-methyl-1-phenyl-2-(2-piperidino-ethylamino)hexan-1-ol dihydrochloride
- Compound 43: (1RS,2SR)-5-methyl-1-phenyl-2-(2-pyrrolidino-ethylamino)hexan-1-ol dihydrochloride
- Compound 44: (1RS,2RS)-5-methyl-1-phenyl-2-(2-pyrrolidino-ethylamino)hexan-1-ol dihydrochloride
- \* Compound 45: (1RS,2SR)-5-methyl-2-[3-(perhydroazepin-1-yl)-propylamino]-1-phenylhexan-1-ol dihydrochloride
- Compound 46: (1RS,2RS)-5-methyl-2-[3-(perhydroazepin-1-yl)-propylamino]-1-phenylhexan-1-ol dihydrochloride

Compound 47: (1RS,2SR)-4-methyl-1-(2-methylphenyl)-2-(3-piperidinopropylamino)pentan-1-ol dihydrochloride

5 Compound 48: (1RS,2RS)-4-methyl-1-(2-methylphenyl)-2-(3-piperidinopropylamino)pentan-1-ol dihydrochloride

Compound 49: (1RS,2SR)-4-methyl-1-(3-methylphenyl)-2-(3-piperidinopropylamino)pentan-1-ol dihydrochloride

10 Compound 50: (1RS,2RS)-4-methyl-1-(3-methylphenyl)-2-(3-piperidinopropylamino)pentan-1-ol dihydrochloride

15 Compound 51: (1RS,2SR)-4-methyl-1-(4-methylphenyl)-2-(3-piperidinopropylamino)pentan-1-ol dihydrochloride

Compound 52: (1RS,2RS)-4-methyl-1-(4-methylphenyl)-2-(3-piperidinopropylamino)pentan-1-ol dihydrochloride

20 Compound 53: (1RS,2SR)-1-(4-methoxyphenyl)-4-methyl-2-(3-piperidinopropylamino)pentan-1-ol dihydrochloride

Compound 54: (1RS,2RS)-1-(4-methoxyphenyl)-4-methyl-2-(3-piperidinopropylamino)pentan-1-ol dihydrochloride

25 Compound 55: (1RS,2SR)-1-(4-fluorophenyl)-4-methyl-2-(3-piperidinopropylamino)pentan-1-ol dihydrochloride

Compound 56: (1RS,2RS)-1-(4-fluorophenyl)-4-methyl-2-(3-piperidinopropylamino)pentan-1-ol dihydrochloride

5 Compound 57: (1RS,2SR)-1-(4-chlorophenyl)-4-methyl-2-(3-piperidinopropylamino)pentan-1-ol dihydrochloride

Compound 58: (1RS,2RS)-1-(4-chlorophenyl)-4-methyl-2-(3-piperidinopropylamino)pentan-1-ol dihydrochloride

10 Compound 59: (1RS,2SR)-5-methyl-1-phenyl-2-(3-piperidinopropylamino)hexan-1-ol methylether dihydrochloride

15 Compound 60: (1RS,2RS)-5-methyl-1-phenyl-2-(3-piperidinopropylamino)hexan-1-ol methylether dihydrochloride

Compound 61: (1RS,2SR)-5-methyl-1-phenyl-2-(3-piperidinopropylamino)hexan-1-ol ethylether dihydrochloride

20 Compound 62: (1RS,2RS)-5-methyl-1-phenyl-2-(3-piperidinopropylamino)hexan-1-ol ethylether dihydrochloride

Compound 63: (1RS,2SR)-2-[methyl-(3-piperidinopropyl)amino]-5-methyl-1-phenylhexan-1-ol dihydrochloride

25 Compound 64: (1RS,2RS)-2-[methyl-(3-piperidinopropyl)amino]-5-methyl-1-phenylhexan-1-ol dihydrochloride

Compound 65: (1RS,2SR)-2-[ethyl-(3-piperidinopropyl)amino]-  
5-methyl-1-phenylhexan-1-ol dihydrochloride

Compound 66: (1RS,2RS)-2-[ethyl-(3-piperidinopropyl)amino]-  
5-methyl-1-phenylhexan-1-ol dihydrochloride

5 The effectiveness of the compounds (I) according to  
the invention was determined with respect to the blocking  
effects against glutamic acid, the neuraxial muscle  
relaxing effects (the rigidity reducing and releasing  
effects on anemic decerebrate rigidity) and the toxicity  
10 levels. The following compounds were used for comparative  
purposes.

Comparative compound 1: (1RS,2SR)-1-phenyl-2-(2-piperidino-  
ethylamino)propan-1-ol dihydro-  
chloride

15 Comparative compound 2: (1RS,2SR)-1-phenyl-2-(2-pyrroli-  
dinoethylamino)propan-1-ol  
dihydrochloride

Comparative compound 3: (1RS,2SR)-2-(2-morpholinoethyl-  
amino)-1-phenylpropan-1-ol  
dihydrochloride

20

Comparative compound 4: (1RS,2SR)-2-(2-dimethylaminoethyl-  
amino)-1-phenylpropan-1-ol  
dihydrochloride

Comparative compound 5: tolperisone hydrochloride

25 Experiment 1

Blocking Effects against Glutamic Acid at  
Neuromuscular Junctions of Crayfish

The method of Ishida et al. [J. Physiol., 298, 301-319 (1980)] and that of Shinozaki et al. [Comp. Biochem. Physiol., 70c, 49-58 (1981)] were followed. The opener muscles of the first walking legs of crayfish were used as experimental materials. The neuromuscular sample was held in a bath in which a physiological solution [composition (mM): NaCl (195), CaCl<sub>2</sub> (18), KCl (5.4), tris-maleate buffer (pH 7.5; 10), glucose (11)] for use with the crayfish was perfused at room temperature and at a constant flow rate. A glass micro-electrode filled with a 3M-KCl solution was inserted in a central part of the muscle fiber to intracellularly record changes in the potential of the muscular cell membrane.

The blocking effect of each test compound against L-glutamic acid was evaluated in terms of the suppression rate to depolarization which was induced by bath-applying L-glutamic acid ( $10^{-4}$  M) in a 5-minute pretreatment with a solution of the test compound ( $2 \times 10^{-4}$  M). The results are shown in Table 1.

Table 1

Test compound	Blocking rate against glutamic acid (%)	Test compound	Blocking rate against glutamic acid (%)
Inventive 1 compound	98	Inventive 35 compound	100
" 3	99	" 37	99
" 5	100	" 39	100
" 6	100	" 41	94
" 7	98	" 43	95
" 11	100	" 45	100
" 13	96	" 47	100
" 15	100	" 49	100
" 16	95	" 51	100
" 17	100	" 52	93
" 18	97	" 53	91
" 19	100	" 55	99
" 20	98	" 57	99
" 21	100	" 58	97
" 22	100	" 59	97
" 23	97	" 65	99
" 25	90	Comparative compound 1	59
" 27	95	" 3	30
" 29	93	" 4	0-50
" 31	91		

Experiment 2Effects on Anemic Decerebrate Rigidity

An anemic decerebrate rigidity sample was prepared principally in accordance with the procedure of Fukuda et al. [Japan. J. Pharmacol., 24, 810 (1974)]. Wistar male rats (body weight: 270 to 350 g) were held on their backs and incised at their cervices under etherization. After the trachea and common carotid arteries were exposed, the trachea was cannulated and the bilateral common carotid arteries and esophagus were then double-ligated and cut.

Thereafter, its occipital bone was exposed through which a circular hole was bored to double-ligate the centrally extending basilar artery. As each rat started coming out of anesthetization, its front limbs became rigid.

Measurement was conducted by recording electromyographic (EMG) response from the muscle of the forelimb (M. triceps brachii) of the rat in the rigid state. The EMG pulses were converted to accumulated values every 10 seconds and recorded as a histogram on a recorder.

The effect of each test compound on the rigidity was evaluated in terms of the suppression rate. This rate was calculated first by determining the area of a decreased EMG pulse part on the histogram upon passage of 10 minutes after administration of a physiological saline solution of each test compound (3 mg/kg) through the femoral vein and then in accordance with the following equation.

$$\text{Suppression rate (\%)} = \frac{a}{A} \times 100$$

where a: EMG pulse area decreased as a result of the administration of the test compound; and

A: EMG pulse area when no test compound was administered (control).

5 The results are shown in Table 2.

Table 2

Test compound	Suppression rate (%)
Inventive compound 3	17.5
" 5	18.5
" 21	65.9
" 22	42.3
" 35	21.6
" 41	23.5
" 43	16.1
" 45	90.5
Comparative compound 2	2.2
" 3	1.0
" 4	1.1
" 5	4.8

Experiment 3Acute Toxicity

Using ddN male mice, the acute toxicity level of each test compound was determined in accordance with an up-and-down method. Some of the test compounds used were dissolved in physiological saline and administered through the caudal vein. The results are shown in Table 3.

Table 3

Test compound	(mg/kg) (iv)
Inventive compound 3	19.2
" 5	22.1
" 15	23.6
" 16	28.8
" 17	15.4
" 19	28.4
" 21	13.6
" 22	19.0
" 35	26.7
" 41	29.5
" 43	31.9
" 45	12.8

The following specific examples and reference examples are given to further illustrate the present invention.

Example 1(1RS,2SR)-5-Methyl-1-phenyl-2-(3-piperidinopropyl-amino)hexan-1-ol dihydrochloride

A mixture of (1RS,2SR)-2-amino-5-methyl-1-5 phenylhexan-1-ol (415 mg, 2 mmol) and 1-(3-chloropropyl)-piperidine (324 mg, 2 mmol) was melted at 70°C in a nitrogen atmosphere. The mixture was heated at 110 to 120°C for 3 hours. After being cooled, the reaction mixture was dissolved with heating in ethanol, followed by addition of concentrated hydrochloric acid (0.2 ml). After the mixture was cooled, precipitated crystals were collected by filtration and washed with ethanol. The crystals were recrystallized from ethanol to obtain 0.27 g of the title compound as white crystals (yield: 33%).

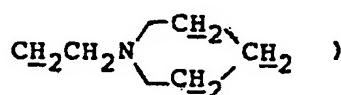
mp: 266-267°C (dec)

IR  $\nu_{\text{max}}^{\text{KBr}}$  (cm<sup>-1</sup>) : 3290, 2945, 2650, 2550, 1590, 1445, 1285, 1130, 1090, 950, 735, 700

free base

IR  $\nu_{\text{max}}^{\text{neat}}$  (cm<sup>-1</sup>): 3290, 2930, 2860, 2800, 1605, 1460, 1445, 1120, 1040, 695

NMR ( $\text{CDCl}_3$ )  $\delta$  : 0.60-0.86 (6H, m,  $\text{CH}(\text{CH}_3)_2$ )  
0.86-1.85 (13H, m,  $\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2$ ,



2.12-2.88 (9H, m,  $\text{CHNCH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)$ )

4.76 (1H, d, J=4Hz, CH-O)

7.24 (5H, m, aromatic protons)

Example 2

(1RS,2RS)-5-Methyl-1-phenyl-2-(3-piperidinopropyl-amino)hexan-1-ol dihydrochloride

A mixture of (1RS,2RS)-2-amino-5-methyl-1-phenyl-hexan-1-ol (1.04 g, 5 mmol) and 1-(3-chloropropyl)-piperidine (0.81 g, 5 mmol) was melted at 70°C in a nitrogen atmosphere. The mixture was then heated at 110 to 10 120°C for 3 hours. After being cooled, the reaction mixture was dissolved with heating in ethanol, followed by addition of concentrated hydrochloric acid (0.5 ml). The resulting mixture was concentrated and the residue was crystallized by treatment with ethanol and hexane. The 15 crystals were collected by filtration, washed with ethanol-hexane and then recrystallized from ethanol-hexane to obtain 1.24 g of the title compound as white crystals (yield: 61%).

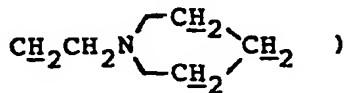
mp: 250-251°C (dec)

20 IR<sub>V</sub> KBr (cm<sup>-1</sup>) : 3310, 2950, 2640, 1590, 1450, 1050, 760,  
max 700

free base

IR<sub>V</sub> neat (cm<sup>-1</sup>): 3300, 2920, 2850, 2800, 1605, 1465, 1445,  
max 1365, 1155, 1120, 1040, 755, 695

25 NMR (CDCl<sub>3</sub>)<sub>δ</sub> : 0.68-0.92 (6H, m, CH(CH<sub>3</sub>)<sub>2</sub>)  
0.92-1.81 (13H, m, CH<sub>2</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>)



- 26 -

2.14-2.94 (9H, m,  $\text{CHNCH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2)_2$ )  
 4.22 (1H, d,  $J=8\text{Hz}$ ,  $\text{CH}_2\text{O}$ )  
 7.24 (5H, m, aromatic protons)

Example 3

5       (1RS,2RS)-1-Phenyl-2-(3-piperidinopropylamino)-  
octan-1-ol dihydrochloride

A mixture of (1RS,2RS)-2-amino-1-phenyloctan-1-ol (1.77 g, 8 mmol) and 1-(3-chloropropyl)piperidine (1.29 g, 8 mmol) was melted at  $70^\circ\text{C}$  in a nitrogen atmosphere. The 10 mixture was then heated at 110 to  $120^\circ\text{C}$  for 3 hours. The reaction mixture was dissolved with heating in ethanol, followed by addition of concentrated hydrochloric acid (0.67 ml). Ethyl acetate was added and the resulting mixture was allowed to stand. Precipitated crystals were 15 collected by filtration and washed with ethyl acetate and then with hexane to obtain 1.96 g of the title compound as white crystals (yield: 59%).

mp: 231-234°C (dec)

IR<sub>v</sub> KBr ( $\text{cm}^{-1}$ ): 3310, 2925, 2700, 1585, 1450, 1055, 760,

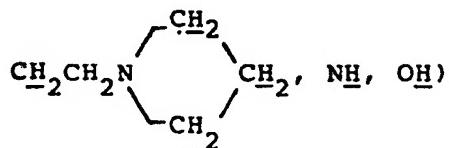
20                   700

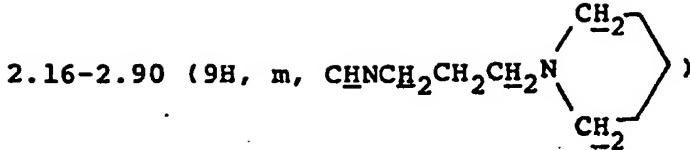
free base

IR<sub>v</sub> neat ( $\text{cm}^{-1}$ ): 3280, 2920, 2850, 2800, 1600, 1465, 1450, 1345, 1150, 1120, 1035, 755, 695

NMR ( $\text{CDCl}_3$ )  $\delta$ : 0.68-1.02 (3H, m,  $\text{CH}_2\text{CH}_3$ )

25                   1.02-1.09 (20H, m,  $(\text{CH}_2)_5\text{CH}_3$ ,





4.24 (1H, d,  $J=8\text{Hz}$ ,  $\text{CH}-\text{O}$ )

7.30 (5H, m, aromatic protons)

Example 4

5      (1RS,2SR)-5-Methyl-1-phenyl-2-(2-piperidinoethyl)-hexan-1-ol dihydrochloride

A mixture of (1RS,2SR)-2-amino-5-methyl-1-phenyl-hexan-1-ol (1.04 g, 5 mmol) and 1-(2-chloroethyl)piperidine (0.74 g, 5 mmol) was melted at  $70^\circ\text{C}$  in a nitrogen 10atmosphere. The mixture was then heated at 110 to  $120^\circ\text{C}$  for 3 hours. After being cooled, the reaction mixture was dissolved in water. The solution was basified with 2N-NaOH and then extracted with ether. The ethereal extract was washed twice with water and once with brine, dried over 15anhydrous sodium sulfate and then evaporated under reduced pressure. The residue was dissolved in acetone (20 ml), followed by addition of concentrated hydrochloric acid (0.74 ml). Precipitated crystals were collected by filtration and washed with acetone. The crystals were 20recrystallized from ethanol (10 ml)-ether (2 ml) to obtain 0.34 g of the title compound as white crystals (yield: 17%).

mp:  $223-224^\circ\text{C}$  (dec)

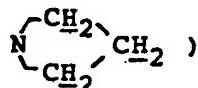
IR  $\nu_{\text{max}}^{\text{KBr}}$  ( $\text{cm}^{-1}$ ): 3260, 2950, 2700, 2470, 1600, 1450, 1200,

25                    1050, 740, 700

free base

IR  $\nu_{\text{max}}$  KBr (cm<sup>-1</sup>): 3180, 2940, 2860, 2820, 1600, 1445, 1250,  
1105, 1050, 760, 695

NMR (CDCl<sub>3</sub>)  $\delta$  : 0.76 (3H, d, J=6Hz, CHCH<sub>3</sub>)  
 5 0.79 (3H, d, J=6Hz, CHCH<sub>3</sub>)  
 1.00-1.77 (11H, m, CH<sub>2</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>,



2.11-2.97 (9H, m, CHNCH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)<sub>2</sub>)

4.73 (1H, d, J=4Hz, CH-O)

10 7.30 (5H, m, aromatic protons)

Example 5

(1RS,2SR)-5-Methyl-1-phenyl-2-(3-piperidinopropyl-  
amino)hexan-1-ol dihydrochloride

A mixture of (1RS,2SR)-2-amino-5-methyl-1-phenyl-  
 15 hexan-1-ol (1.04 g, 5 mmol) and 1-(3-chloropropyl)-  
 piperidine (0.81 g, 5 mmol) in benzene (10 ml) was refluxed  
 for 40 hours. After being cooled, the reaction mixture was  
 concentrated under reduced pressure. The residue was  
 dissolved in ethanol (10 ml), followed by addition of  
 20 6N-HCl in EtOH (2 ml). Precipitated crystals were  
 collected by filtration and then recrystallized from  
 ethanol to obtain 1.15 g of the title compound as white  
 crystals (yield: 57%).

mp: 266-267°C (dec)

25

Example 6

(1RS,2SR)-5-Methyl-1-phenyl-2-(3-piperidinopropyl-

(1RS,2SR)-2-amino-5-methyl-1-phenyl-

A mixture of (1RS,2SR)-2-amino-5-methyl-1-phenyl-hexan-1-ol (1.04 g, 5 mmol), 3-piperidinopropyl tosylate hydrochloride (2.00 g, 6 mmol) and sodium bicarbonate (1.05 g, 12.5 mmol) in ethanol (10 ml) was refluxed for 1 hour.

After cooling, to the reaction mixture were added ether (100 ml), water (50 ml) and 2N-NaOH (5 ml) and the resulting mixture was well shaken. The ethereal layer was separated and washed three times with water, then once with 10brine, followed by drying and subsequent concentration under reduced pressure. The residue was dissolved in ethanol and to the solution was added 6N-HCl in EtOH (1.5 ml). Precipitated crystals were collected by filtration and then recrystallized from ethanol to obtain 0.73 g of 15the title compound as white crystals (yield: 36%).

mp: 266-267°C (dec)

Example 7(1RS,2SR)-5-Methyl-1-phenyl-2-(3-piperidinopropyl-  
amino)hexan-1-ol methyl ether dihydrochloride

To a solution of (1RS,2SR)-5-methyl-1-phenyl-2-(3-piperidinopropylamino)hexan-1-ol (1.66 g, 5 mmol) in toluene (25 ml) was added sodium hydride (0.14 g, 6 mmol) and the mixture was refluxed for 1 hour. To the reaction mixture was added methyl tosylate (1.12 g, 6 mmol) and the 25resulting mixture was refluxed for further 1 hour. After being cooled, the mixture was washed twice with water and once with brine, dried over anhydrous sodium sulfate and

then concentrated under reduced pressure. The residue was purified by neutral alumina column chromatography (alumina: 40 g, eluent: chloroform) to give 1.1 g of oily matter. To a solution of the matter in acetone (20 ml) was added 5 concentrated hydrochloric acid (0.1 ml) and the mixture was concentrated under reduced pressure. The residue was recrystallized from acetone (10 ml)-ethanol (0.2 ml) to obtain 0.45 g of the title compound as white crystals (yield: 21%).

10 mp: 138-141°C

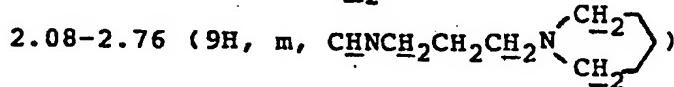
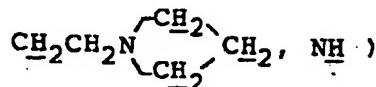
IR  $\nu$  KBr (cm<sup>-1</sup>) : 3360, 2940, 2640, 1570, 1450, 1120, 1095, 15 1060, 1010, 740, 695

free base

IR  $\nu$  neat (cm<sup>-1</sup>): 2940, 2860, 2810, 1460, 1445, 1150, 1120,

15 1100, 695

NMR (CDCl<sub>3</sub>)  $\delta$  : 0.70-0.96 (6H, m, CH(CH<sub>3</sub>)<sub>2</sub>)  
1.00-1.70 (14H, m, (CH<sub>2</sub>)<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>,



20 3.24 (3H, s, OCH<sub>3</sub>)

4.17 (1H, d, J=5Hz, CH-O)

7.30 (5H, m, aromatic protons)

Example 8

(1RS,2SR)-2-[Ethyl-(3-piperidinopropyl)amino]-5-

25 methyl-1-phenylhexan-1-ol dihydrochloride

To a cooled mixture of (1RS,2SR)-5-methyl-1-phenyl-2-(3-piperidinopropylamino)hexan-1-ol (821 mg, 2.47 mmol)

in ether (36 ml) and a 10% NaOH aqueous solution (15 ml) was added dropwise a solution of acetyl chloride (0.21 g, 2.7 mmol) in benzene. The organic layer was separated, washed with brine, dried over anhydrous sodium sulfate and 5 then concentrated under reduced pressure. The residue was purified by silica gel column chromatography to obtain an N-acetylated product ( $\text{IR}^{\nu}$  <sub>max</sub> <sup>neat</sup>:  $1620 \text{ cm}^{-1}$ ) of the starting material. To a cooled solution of such compound in tetrahydrofuran (12.4 ml) was added lithium aluminum 10 hydride (0.47 g) and the reaction mixture was refluxed for 3 hours. Ethyl acetate was added with cooling to the mixture to consume excess lithium aluminum hydride and the mixture was then poured into an aqueous saturated sodium sulfate solution. The organic layer was separated by 15 decantation, dried over anhydrous sodium sulfate and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: chloroform/methanol = 25/1) to give a free base of the title compound. To a solution of the compound in ethanol 20 was added in excess 6N-HCl in EtOH and the mixture was concentrated under reduced pressure. The residue was crystallized by treatment with ether, followed by recrystallization from ethanol-ethyl acetate to obtain 510 mg of the title compound as white crystals (yield: 48%).

25 mp: 190-193°C

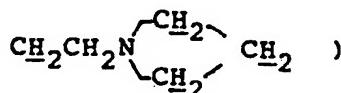
IR $\nu$  <sub>max</sub> <sup>KBr</sup> ( $\text{cm}^{-1}$ ): 3400, 2950, 2870, 2660, 1450, 1420, 1090, 1050, 1030, 735, 700

free base

IR<sub>v</sub> neat (cm<sup>-1</sup>): 2940, 2870, 2820, 1490, 1465, 1445, 1380,  
max 1365, 1345, 1155, 1125, 1065, 1040, 760,  
700

<sup>1</sup>H NMR (CDCl<sub>3</sub>)<sup>δ</sup> : 0.80 (6H, d, J=6Hz, CH(CH<sub>3</sub>)<sub>2</sub>)  
1.02 (3H, t, J=7Hz, NCH<sub>2</sub>CH<sub>3</sub>)

1.10-1.82 (13H, m, (CH<sub>2</sub>)<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>,



1.90-2.94 (11H, m, CHNCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)<sub>2</sub>) )

10 4.76 (1H, d, J=4Hz, CH-O)

5.40 (1H, broad s, OH)

7.04-7.46 (5H, m, aromatic protons)

Example 9

(1RS,2RS)-5-Methyl-1-phenyl-2-(3-piperidinopropyl-  
15 amino)hexan-1-ol dihydrochloride

A mixture of 2-bromo-5-methyl-1-phenylhexan-1-ol  
(prepared from 2-bromo-5-methyl-1-phenylhexan-1-one by  
usual NaBH<sub>4</sub>-reduction) (1.0 g, 3.69 mmol) and 1-(3-amino-  
propyl)piperidine (1.05 g, 7.38 mmol) was heated at 110°C  
20 for 4 hours in a nitrogen atmosphere. After being cooled,  
the reaction mixture was dissolved in 1N-HCl (50 ml) and  
the solution was washed with ether. The aqueous layer was  
basified with 1N-NaOH and then extracted twice with ether.  
The combined ethereal extract was washed three times with  
25 water, dried over anhydrous sodium sulfate and evaporated

under reduced pressure. The residue was purified by preparative TLC to give pale yellow oily matter. To a solution of the matter in ethanol was added in excess 18% HCl in EtOH and the resulting mixture was evaporated under 5 reduced pressure. The residue was dissolved with heating in ethanol (15 ml) and to the mixture was then added 10 ml of acetone. The mixture was stirred at room temperature. Precipitated crystals were collected by filtration to obtain 0.52 g of the title compound (yield: 35%).

10 mp: 250-251°C (dec)

Example 10

(1RS,2SR)-5-Methyl-1-phenyl-2-(3-piperidinopropyl-amino)hexan-1-ol dihydrochloride

To a solution of 1-(3-aminopropyl)piperidine (0.14 g, 15 1 mmol) in chloroform (2 ml) was added a solution of 2-bromo-5-methyl-1-phenylhexan-1-one [bp: 128-130°C/2.5 mmHg; prepared from 5-methyl-1-phenylhexan-1-one by usual bromination] (0.54 g, 2 mmol) in chloroform (4 ml) and the mixture was stirred for 4 hours at room temperature in a 20 nitrogen atmosphere. The reaction mixture was concentrated below 30°C under reduced pressure. To a solution of the residue in methanol (4 ml) was added sodium borohydride (0.08 g) with ice-cooling and the mixture was stirred for 1 hour at room temperature. The reaction mixture was 25 concentrated below 30°C under reduced pressure. The residue was dissolved in 1N-HCl and the solution was washed twice with ethyl acetate, basified with 1N-NaOH and then

extracted with ether. The ethereal extract was washed with water and then with brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to obtain 0.18 g of pale yellow oil. To a solution of the oil in 5 ethanol (4 ml) was added 0.22 g of 18% HCl in EtOH and the mixture was allowed to stand overnight. Precipitated crystals were collected by filtration to obtain 0.11 g of the title compound as white crystals (yield: 27%).  
mp: 266-267°C (dec)

10

Example 11

(1RS,2SR)-5-Methyl-1-phenyl-2-(3-piperidinopropyl-  
amino)hexan-1-ol dihydrochloride

To a refluxing mixture of 1-(3-aminopropyl)piperidine (284 mg, 2 mmol), sulfurous acid (6% SO<sub>2</sub> aqueous solution) 15 (1.1 ml) and zinc dust (200 mg) in methanol (2.5 ml) was added dropwise over a period of 1 hour a solution of 5-methyl-1-phenylhexane-1,2-dione [bp: 104-107°C/2 mmHg; prepared from 2-bromo-5-methyl-1-phenylhexan-1-one by a known method {N. Kornblum and H. W. Frazier: J. Am. Chem. 20 Soc., 88, 865 (1966)}] (275 mg, 1.35 mmol) in methanol (1.0 ml). Thereafter, 200 mg of zinc dust and 1.8 ml of sulfurous acid were freshly added to the mixture and the resulting mixture was refluxed for further 2 hours. After cooling, methanol was added to the mixture and insoluble 25 material was removed by filtration. The filtrate was concentrated under reduced pressure and the residue was dissolved in 2N-HCl. The resulting solution was washed

three times with ether and then basified with an aqueous sodium hydroxide solution, followed by extraction with ether. The combined ethereal extract was washed twice with water, dried over anhydrous sodium sulfate and evaporated 5 under reduced pressure to give 0.43 g of oily matter. To an ethanol solution of the matter was added 6N-HCl in EtOH (0.64 ml) and the solution was allowed to stand. Precipitated crystals were collected by filtration and washed with ethanol to obtain 170 mg of the title compound 10 as white crystals (yield: 31%).

mp: 266-267°C (dec)

Example 12

(1RS,2SR)-5-Methyl-1-phenyl-2-(3-piperidinopropyl-amino)hexan-1-ol dihydrochloride

15 A mixture of 1-hydroxy-5-methyl-1-phenylhexan-2-one [bp: 111-115°C/2 mmHg; prepared by a known method, e.g. D. H. Hey: J. Chem. Soc., 1232 (1930)] (413 mg, 2 mmol), 1-(3-aminopropyl)piperidine (285 mg, 2 mmol) and 0.4 g of 5% Pd/C in methanol (20 ml) was shaken in a shaker bomb at 20 4 atms of hydrogen for 16 hours at room temperature. The catalysts were removed by filtration and the filtrate was concentrated under reduced pressure. The residue was dissolved in ether and the solution was washed twice with water, dried and then evaporated under reduced pressure. 25 The residue was dissolved in ethanol (12 ml) and to the solution was added 0.7 ml of 6N-HCl in EtOH. The resulting solution was allowed to stand. Precipitated crystals were

collected by filtration to obtain 340 mg of the title compound (yield: 42%).

mp: 266-267°C (dec)

Example 13

5       (1RS,2SR)-5-Methyl-1-phenyl-2-(3-piperidinopropyl-amino)hexan-1-ol dihydrochloride

To a solution of 1-(3-aminopropyl)piperidine (285 mg, 2 mmol) in methanol (6 ml) was added 0.1 ml of 6.8N-HCl in MeOH, 1-hydroxy-5-methyl-1-phenylhexan-2-one (413 mg, 2 mmol) and sodium cyanoborohydride (126 mg, 2 mmol). The reaction mixture was stirred for 19 hours at room temperature. The mixture was concentrated under reduced pressure and to the residue was added 1N-HCl and ether. The aqueous layer was separated, basified with a 10% NaOH 15 aqueous solution and then extracted three times with ether. The combined ethereal extract was washed twice with water, dried over anhydrous sodium sulfate and then evaporated under reduced pressure. The residue was dissolved in ethanol (12 ml). To the solution was added 0.70 ml of 6N-HCl in EtOH and the resulting mixture was allowed to stand. Precipitated crystals were collected by filtration 20 to obtain 228 mg of the title compound (yield: 28%).

mp: 266-267°C (dec)

Example 14

25       (1RS,2SR)-5-Methyl-1-phenyl-2-(3-piperidinopropyl-amino)hexan-1-ol dihydrochloride

To a solution of sodium hydroxide (1.44 g) in water

(6.6 ml) was added a solution of (4RS,5SR)-4-(3-methylbutyl)-5-phenyl-3-(3-piperidinopropyl)-1,3-oxazolidin-2-one (717 mg, 2 mmol) in ethanol (53 ml), the mixture was refluxed for 26 hours and then concentrated under reduced pressure. Water was added to the residue and the mixture was extracted three times with chloroform. The combined extract was dried over anhydrous sodium sulfate and then concentrated under reduced pressure. The residue was dissolved in ethanol (15 ml) and concentrated hydrochloric acid (0.34 ml) was added. Precipitated crystals were collected by filtration, washed first with ethanol and then with hexane to obtain 0.75 g of the title compound as white crystals (yield: 78%).

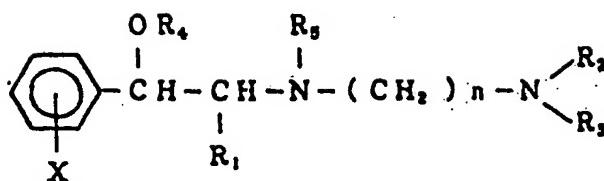
mp: 266-267°C (dec)

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Examples 15-55

The compounds listed in Table 4-A were prepared in a similar manner as described in Examples 1 to 4 and the physical data of these compounds were shown in Table 4-B.

Table 4-A



Example	Configuration	R <sub>1</sub>	N <sup>R<sub>2</sub></sup> <sub>R<sub>3</sub></sub>	R <sub>4</sub>	R <sub>5</sub>	X	n
15	1RS, 2SR	-(CH <sub>2</sub> ) <sub>2</sub> CH <sub>3</sub>	N	H	H	H	3
16	1RS, 2RS	-(CH <sub>2</sub> ) <sub>2</sub> CH <sub>3</sub>	N	H	H	H	3
17	1RS, 2SR	-(CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub>	N	H	H	H	3
18	1RS, 2RS	-(CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub>	N	H	H	H	3
19	1RS, 2SR	-(CH <sub>2</sub> ) <sub>4</sub> CH <sub>3</sub>	N	H	H	H	3
20	1RS, 2RS	-(CH <sub>2</sub> ) <sub>4</sub> CH <sub>3</sub>	N	H	H	H	3
21	1RS, 2SR	-(CH <sub>2</sub> ) <sub>5</sub> CH <sub>3</sub>	N	H	H	H	3
22	1RS, 2SR	-CH(CH <sub>3</sub> ) <sub>2</sub>	N	H	H	H	3
23	1RS, 2RS	-CH(CH <sub>3</sub> ) <sub>2</sub>	N	H	H	H	3
24	1RS, 2SR	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	N	H	H	H	3
25	1RS, 2RS	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	N	H	H	H	3
26	1R, 2S	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	N	H	H	H	3
27	1S, 2R	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	N	H	H	H	3
28	1S, 2S	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	N	H	H	H	3

Example	Configuration	R <sub>1</sub>	N R <sub>2</sub> R <sub>3</sub>	R <sub>4</sub>	R <sub>5</sub>	X	n
29	1R, 2R	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	N Cyclohexyl	H	H	H	3
30	1RS, 2SR	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	N Cyclohexyl	H	H	H	3
31	1RS, 2RS	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	N Cyclohexyl	H	H	H	3
32	1RS, 2SR	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	N Cyclopentyl	H	H	H	3
33	1RS, 2RS	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	N Cyclopentyl	H	H	H	3
34	1RS, 2SR	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	N CH <sub>3</sub> CH <sub>3</sub>	H	H	H	3
35	1RS, 2RS	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	N CH <sub>3</sub> CH <sub>3</sub>	H	H	H	3
36	1RS, 2SR	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	N Cyclohexyl	H	H	H	2
37	1RS, 2RS	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	N Cyclohexyl	H	H	H	2
38	1RS, 2SR	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	N Cyclohexyl	H	H	H	2
39	1RS, 2RS	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	N Cyclohexyl	H	H	H	2
40	1RS, 2SR	-(CH <sub>2</sub> ) <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	N Cyclohexyl	H	H	H	3

Example	Configuration	R <sub>1</sub>	N R <sub>2</sub> R <sub>3</sub>	R <sub>4</sub>	R <sub>5</sub>	X	n
41	1RS, 2SR	-(CH <sub>2</sub> ) <sub>2</sub> CH CH <sub>3</sub> CH <sub>3</sub>	N O	H	H	H	3
42	1RS, 2SR	-(CH <sub>2</sub> ) <sub>2</sub> CH CH <sub>3</sub> CH <sub>3</sub>	N CH <sub>3</sub> CH <sub>3</sub>	H	H	H	3
43	1RS, 2SR	-(CH <sub>2</sub> ) <sub>2</sub> CH CH <sub>3</sub> CH <sub>3</sub>	N C H <sub>3</sub>	H	H	H	2
44	1RS, 2SR	-(CH <sub>2</sub> ) <sub>2</sub> CH CH <sub>3</sub> CH <sub>3</sub>	N C H <sub>3</sub>	H	H	H	3
45	1RS, 2SR	-CH <sub>2</sub> CH CH <sub>3</sub> CH <sub>3</sub>	N C H <sub>3</sub>	H	H	2-CH <sub>3</sub>	3
46	1RS, 2SR	-CH <sub>2</sub> CH CH <sub>3</sub> CH <sub>3</sub>	N C H <sub>3</sub>	H	H	3-CH <sub>3</sub>	3
47	1RS, 2RS	-CH <sub>2</sub> CH CH <sub>3</sub> CH <sub>3</sub>	N C H <sub>3</sub>	H	H	3-CH <sub>3</sub>	3
48	1RS, 2SR	-CH <sub>2</sub> CH CH <sub>3</sub> CH <sub>3</sub>	N C H <sub>3</sub>	H	H	4-CH <sub>3</sub>	3
49	1RS, 2RS	-CH <sub>2</sub> CH CH <sub>3</sub> CH <sub>3</sub>	N C H <sub>3</sub>	H	H	4-CH <sub>3</sub>	3
50	1RS, 2SR	-CH <sub>2</sub> CH CH <sub>3</sub> CH <sub>3</sub>	N C H <sub>3</sub>	H	H	4-OCH <sub>3</sub>	3
51	1RS, 2SR	-CH <sub>2</sub> CH CH <sub>3</sub> CH <sub>3</sub>	N C H <sub>3</sub>	H	H	4-F	3
52	1RS, 2RS	-CH <sub>2</sub> CH CH <sub>3</sub> CH <sub>3</sub>	N C H <sub>3</sub>	H	H	4-F	3

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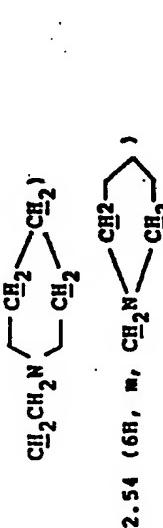
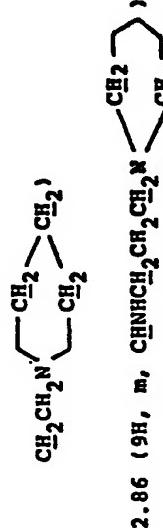
Example	Configuration	R <sub>1</sub>	N R <sub>2</sub> R <sub>3</sub>	R <sub>4</sub>	R <sub>5</sub>	X	n
53	1RS, 2SR	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	N Cyclohexyl	H	H	4-Cl	3
54	1RS, 2RS	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	N Cyclohexyl	H	H	4-Cl	3
55	1RS, 2SR	-(CH <sub>2</sub> ) <sub>7</sub> CH <sub>3</sub>	N Cyclohexyl	H	H	H	3

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Table 4-B

Example	mp (dihydrochloride)	KBr IR: $\nu_{\text{max}}$ (cm $^{-1}$ ) (dihydrochloride)	NMR ( $\delta$ : CDCl $_3$ ) (free base) or $[\alpha]_D$ (dihydrochloride)
15	259-261°C (dec) (EtOH)	3300, 2940, 2775, 2550, 1585, 1445, 1285, 1085, 1045, 955, 730, 705	0.64-0.92 (3H, m, CH $_2$ CH $_3$ ) 0.96-1.68 (12H, m (CH $_2$ ) $_2$ CH $_3$ ,  $\text{CH}_2\text{CH}_2\text{N} \left[ \begin{array}{c} \text{CH}_2 \\   \\ \text{CH}_2 \end{array} \right] \text{CH}_2 \text{CH}_2$ )  2.12-2.52 (6H, m, CH $_2$ N $\left[ \begin{array}{c} \text{CH}_2 \\   \\ \text{CH}_2 \end{array} \right]$ ) 2.56-2.88 (3H, m, CHNHCH $_2$ ) 4.10 (2H, broad s, NH, OH) 4.77 (1H, d, J = 4 Hz, CH-O) 7.29 (5H, m, aromatic protons)
16	223-227°C (dec) (EtOH-Et $_2$ O)	3325, 2930, 2680, 1590, 1450, 1050, 765, 700	0.70-1.00 (3H, m, CH $_2$ CH $_3$ ) 1.08-1.84 (12H, m (CH $_2$ ) $_2$ CH $_3$ ,  $\text{CH}_2\text{CH}_2\text{N} \left[ \begin{array}{c} \text{CH}_2 \\   \\ \text{CH}_2 \end{array} \right] \text{CH}_2$ )  2.16-2.88 (9H, m, CHNHCH $_2$ CH $_2$ CH $_2$ N $\left[ \begin{array}{c} \text{CH}_2 \\   \\ \text{CH}_2 \end{array} \right]$ ) 4.24 (1H, d, J = 8 Hz, CH-O) 7.31 (5H, m, aromatic protons)

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17 257-258°C (dec) (MeOH)	<p>3280, 2940, 2650, 2550, 1590, 1440, 1280, 1090, 950, 720, 700</p> <p>0.63-0.96 (3H, m, CH<sub>2</sub>CH<sub>3</sub>) 0.96-1.86 (14H, m (CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>)</p>  <p>2.14-2.54 (6H, m, CH<sub>2</sub>N(CH<sub>2</sub>)<sub>2</sub>CH<sub>2</sub>) 2.54-2.91 (3H, m, CHNHCH<sub>2</sub>) 3.0-5.3 (2H, broad s, NH, OH) 4.78 (1H, d, J = 4 Hz, CH-O) 7.30 (5H, m, aromatic protons)</p>
18 232-235°C (dec) (EtOH-BtOAc)	<p>3290, 2930, 2640, 1585, 1445, 1040, 755, 695</p> <p>0.62-0.99 (3H, m, CH<sub>2</sub>CH<sub>3</sub>) 0.99-1.80 (14H, m (CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>)</p>  <p>2.13-2.86 (9H, m, CHNHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)<sub>2</sub>CH<sub>2</sub>) 4.24 (1H, d, J = 8 Hz, CH-O) 7.30 (5H, m, aromatic protons)</p>

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19	261-262°C (dec) (EtOH)	3290, 2940, 2870, 2660, 2550, 1590, 1445, 1290, 1090, 950, 750, 720, 700	<p>0.60-1.85 (19H, m, <math>(\underline{\text{CH}_2})_4 \text{CH}_3</math>,</p> <p><chem>CCN(CC(C)C)CC(C)C</chem></p> <p>2.12-2.52 (6H, m, <math>\text{CH}_2\text{N}(\text{CH}_2)\text{CH}_2</math>)</p> <p>2.52-2.87 (3H, m, <math>\text{CH}_2\text{NHCH}_2</math>)</p> <p>4.77 (1H, d, J = 4 Hz, <math>\text{CH}_2\text{O}</math>)</p> <p>7.29 (5H, m, aromatic protons)</p>
20	238-241°C (dec) (EtOH-EtOAc)	3330, 2940, 2690, 2540, 1585, 1445, 1050, 760, 700	<p>0.68-1.00 (3H, m, <math>\text{CH}_2\text{CH}_3</math>)</p> <p>1.00-1.84 (16H, m <math>(\underline{\text{CH}_2})_4 \text{CH}_3</math>,</p> <p><chem>CCN(CC(C)C)CC(C)C</chem></p> <p>2.12-2.86 (9H, m, <math>\text{CH}_2\text{NHCH}_2\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2)\text{CH}_2</math>)</p> <p>3.20 (2H, broad s, <math>\text{OH}</math>, NH)</p> <p>4.25 (1H, d, J = 8 Hz, <math>\text{CH}_2\text{O}</math>)</p> <p>7.30 (5H, m, aromatic protons)</p>

21	253-255°C (dec) (EtOH)	3280, 2930, 2850, 2670, 2550, 1585, 1445, 1280, 1040, 955, 700	0.68-0.96 (3H, m, CH <sub>2</sub> CH <sub>3</sub> ) 0.96-1.86 (20H, m (CH <sub>2</sub> ) <sub>5</sub> CH <sub>3</sub> , CH <sub>2</sub> CH <sub>2</sub> N(CH <sub>2</sub> ) <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> , NH, OH) 2.12-2.54 (6H, m, CH <sub>2</sub> N(CH <sub>2</sub> ) <sub>2</sub> CH <sub>2</sub> ) 2.54-2.92 (3H, m, CHNHCH <sub>2</sub> ) 4.78 (1H, d, J = 4 Hz, CH <sub>2</sub> -O) 7.29 (5H, m, aromatic protons)
22	210-212°C (dec) (EtOH)	3290, 2940, 2670, 2555, 1600, 1445, 1285, 1125, 1060, 1000, 750, 700	0.87 (6H, d, J = 7 Hz, CH(CH <sub>3</sub> ) <sub>2</sub> ) 1.17-1.92 (9H, m CH (CH <sub>3</sub> ) <sub>2</sub> , CH <sub>2</sub> CH <sub>2</sub> N(CH <sub>2</sub> ) <sub>2</sub> CH <sub>2</sub> ) 2.08-2.86 (9H, m, CHNHCH <sub>2</sub> CH <sub>2</sub> N(CH <sub>2</sub> ) <sub>2</sub> CH <sub>2</sub> ) 4.77 (1H, d, J = 5 Hz, CH <sub>2</sub> -O) 7.00-7.45 (5H, m, aromatic protons)

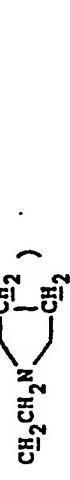
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23	238-240°C (dec) (EtOH)	3270, 2930, 2650, 2520, 1585, 1450, 1020, 760, 700	<p>0.92 (3H, d, J = 7 Hz, CHCH<sub>3</sub>)          0.96 (3H, d, J = 7 Hz, CHCH<sub>3</sub>)          1.17 - 1.95 (9H, m, CH(CH<sub>3</sub>)<sub>2</sub>,  <chem>CH2CH2N\CH2\CH2\CH2&gt;</chem>)</p> <p>2.04-2.89 (9H, m, CHNHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N&lt;chem&gt;CH2&lt;/chem&gt;&gt;CH<sub>2</sub>)</p> <p>4.32 (1H, d, J = 6 Hz, CH-O)</p> <p>7.00-7.45 (5H, m, aromatic protons)</p>
24	268-270°C (dec) (EtOH)	3330, 2945, 2870, 2680, 2560, 1580, 1450, 1430, 1400, 1370, 1285, 1145, 1090, 1070, 1040, 965, 955, 755, 705	<p>0.71 (3H, d, J = 6 Hz, CHCH<sub>3</sub>)          0.82 (3H, d, J = 7 Hz, CHCH<sub>3</sub>)          0.86 - 1.90 (11H, m, CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>,  <chem>CH2CH2N\CH2\CH2\CH2&gt;</chem>)</p> <p>2.16-2.52 (6H, m, CH<sub>2</sub>N&lt;chem&gt;CH2&lt;/chem&gt;&gt;CH<sub>2</sub>)</p> <p>2.58-2.92 (3H, m, CHNHCH<sub>2</sub>)</p> <p>4.10 (2H, broad s, NH, OH)</p> <p>4.80 (1H, d, J = 4 Hz, CH-O)</p> <p>7.29 (5H, m, aromatic protons)</p>

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25	244-246°C (dec) (EtO <sub>2</sub> H-EtOAc)	3360, 3030, 2940, 2870, 2680, 2550, 1575, 1480, 1450, 1430, 1410, 1385, 1365, 1285, 1080, 1070, 1050, 960, 950, 760, 700	0.76 (3H, d, J = 6 Hz, CHCH <sub>3</sub> ) 0.86 (3H, d, J = 6 Hz, CHCH <sub>3</sub> ) 1.04 - 1.84 (11H, m, CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub> , CH <sub>2</sub> CH <sub>2</sub> N(CH <sub>2</sub> ) <sub>2</sub> CH <sub>2</sub> )
26	266-267°C (dec) (EtOH)	3330, 2940, 2870, 2660, 2540, 1605 1445, 1430, 1400, 1285, 1140, 1090, 1065, 1030, 960, 945, 745, 700	[\alpha] <sub>D</sub> -24.9° (C0.62, MeOH) 4.23 (1H, d, J = 7 Hz, CH <sub>2</sub> -O) 7.31 (5H, m, aromatic protons)
27	266-267°C (dec) (EtOH)	3330, 2940, 2870, 2660, 2540, 1605 1445, 1430, 1400, 1285, 1140, 1090, 1065, 1030, 960, 945, 745, 700	[\alpha] <sub>D</sub> +25.3° (C0.60, MeOH)
28	234-236°C (dec) (EtOH-EtOAc)	3300, 2950, 2700, 2550, 1570, 1450, 1430, 1390, 1370, 1280, 1200, 1140, 1080, 1045, 950, 760, 700	[\alpha] <sub>D</sub> +24.3° (C0.60, MeOH)
29	230-232°C (dec) (EtOH-EtOAc)	3300, 2950, 2700, 2550, 1570, 1450, 1430, 1390, 1370, 1280, 1200, 1140, 1080, 1045, 950, 760, 700	[\alpha] <sub>D</sub> <sup>23</sup> -24.3° (C0.60, MeOH)

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30	240-241°C (dec) (EtOH)	3320, 2950, 2680, 1595, 1445, 750, 695	0.71 (3H, d, J = 6 Hz, CH <u>CH</u> <sub>3</sub> ) 0.82 (3H, d, J = 7 Hz, CH <u>CH</u> <sub>3</sub> ) 0.88 - 1.96 (9H, m, CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub> ,  2.04-2.95 (9H, m, CHNH <u>CH</u> <sub>2</sub> CH <sub>2</sub> N <u>CH</u> <sub>2</sub>  )
31	226.5-228.5°C (dec) (EtOH-EtOAc)	3280, 2960, 2685, 1580, 1450, 1040, 760, 695	0.75 (3H, d, J = 6 Hz, CH <u>CH</u> <sub>3</sub> ) 0.84 (3H, d, J = 6 Hz, CH <u>CH</u> <sub>3</sub> ) 0.95 - 1.96 (9H, m, CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub> ,  2.00-2.88 (9H, m, CHNH <u>CH</u> <sub>2</sub> CH <sub>2</sub> N <u>CH</u> <sub>2</sub>  )

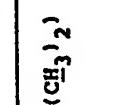
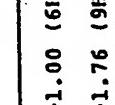
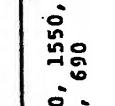
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32	269-270°C (dec) (EtOH)	3275, 2940, 2665, 2600, 1590, 1440, 1255, 1110, 1090, 1045, 755, 705	0.72 (3H, d, J = 6 Hz, CHCH <sub>3</sub> ) 0.83 (3H, d, J = 6 Hz, CHCH <sub>3</sub> ) 0.88-1.86 (5H, m, CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub> )  Cl <sub>2</sub> CH <sub>2</sub> N <sub>2</sub> O <sub>2</sub>	2.25-2.56 (6H, m, CH <sub>2</sub> N <sub>2</sub> O <sub>2</sub> ) 2.63-2.92 (3H, m, CHNHCH <sub>2</sub> ) 3.0-4.6 (2H, broad s, NH, OH) 3.69 (4H, t, J = 5 Hz, N-CH <sub>2</sub> -O) 4.79 (1H, d, J = 4 Hz, CH-O) 7.29 (5H, m, aromatic protons)
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33	250-252°C (dec) (EtOH)	3300, 2950, 2600, 1580, 1450, 1260, 1110, 1085, 1040, 760, 700	0.76 (3H, d, J = 6 Hz, CH <sub>2</sub> <sup>13</sup> <sub>3</sub> ) 0.85 (3H, d, J = 6 Hz, CH <sub>2</sub> <sup>13</sup> <sub>3</sub> ) 1.03-1.80 (5H, m, CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub> , CH <sub>2</sub> CH <sub>2</sub> N(=O)C <sub>2</sub> H <sub>5</sub> )
34	255-256°C (dec) (EtOH-n-Hexane)	3300, 2960, 2760, 2645, 2510, 1590, 1455, 1430, 1105, 1065, 1045, 755 700	2.22-2.88 (9H, m, CHNHCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> N(=O)C <sub>2</sub> H <sub>5</sub> ) 3.55-3.86 (4H, m, N(CH <sub>2</sub> ) <sub>2</sub> O) 4.24 (1H, d, J = 7 Hz, CH-O) 2.4-6.4 (2H, broad s, NH, OH) 7.30 (5H, m, aromatic protons)
35	243-244°C (dec) (EtOH-n-hexane)	3300, 2960, 2670, 1590, 1465, 1450, 1040, 760, 700	0.64-0.88 (6H, m, CH(CH <sub>3</sub> ) <sub>2</sub> ) 0.88-2.88 (12H, m, CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub> , CHNHCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> N(=O)C <sub>2</sub> H <sub>5</sub> , NH, OH) 2.22 (6H, s, N(CH <sub>3</sub> ) <sub>2</sub> ) 4.81 (1H, d, J = 4 Hz, CH-O) 7.29 (5H, m, aromatic protons)

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36	234-235°C (dec) (EtOH-n-hexane)	3300, 2960, 2720, 2460, 1600, 1460, 1445, 750, 705	0.64-0.88 (6H, m, CH(CH <sub>3</sub> ) <sub>2</sub> ) 0.88-1.76 (9H, m, 
			2.10-3.20 (11H, m, 
37	238-239°C (dec) (EtOH-n-hexane)	3270, 2955, 2720, 2480, 1560, 1550, 1445, 1385, 1055, 1010, 760, 690	0.64-1.00 (6H, m, CH(CH <sub>3</sub> ) <sub>2</sub> ) 1.00-1.76 (9H, m, 
			2.10-2.90 (9H, m, 

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38	236-237°C (dec) (EtOH)	3290, 2960, 2650, 2460, 1595, 1460, 1445, 1090, 1025, 750, 705 0.75 (3H, d, J = 7 Hz, CHCH <sub>3</sub> ) 0.83 (3H, d, J = 7 Hz, CHCH <sub>3</sub> ) 0.90-2.00 (7H, m,	$\text{CH}_2\text{CH}(\text{CH}_3)_2, \text{N} \left( \begin{array}{c} \text{CH}_2 \\   \\ \text{CH}_2-\text{CH}_2 \end{array} \right),$ $\text{CHNHCH}_2\text{CH}_2\text{N} \left( \begin{array}{c} \text{CH}_2 \\   \\ \text{CH}_2-\text{CH}_2 \end{array} \right),$ 2.10-3.00 (9H, m, $\text{CH}_2\text{CH}(\text{CH}_3)_2, \text{N} \left( \begin{array}{c} \text{CH}_2 \\   \\ \text{CH}_2-\text{CH}_2 \end{array} \right),$ 3.0-5.5 (2H, broad s, NH, OH) 4.75 (1H, d, J = 4 Hz, CH-O) 7.30 (5H, m, aromatic protons) $\text{CH}_2\text{CH}(\text{CH}_3)_2, \text{N} \left( \begin{array}{c} \text{CH}_2 \\   \\ \text{CH}_2-\text{CH}_2 \end{array} \right),$ 2.10-2.90 (9H, m, $\text{CH}_2\text{CH}(\text{CH}_3)_2, \text{N} \left( \begin{array}{c} \text{CH}_2 \\   \\ \text{CH}_2-\text{CH}_2 \end{array} \right),$ 3.2-6.4 (2H, broad s, NH, OH) 4.22 (1H, d, J = 7 Hz, CH-O) 7.29 (5H, m, aromatic protons)
39	201-203°C (acetone)	3255, 2960, 2600, 1565, 1450, 1060, 1020, 765, 700 0.75 (3H, d, J = 6 Hz, CHCH <sub>3</sub> ) 0.84 (3H, d, J = 7 Hz, CHCH <sub>3</sub> ) 0.93-2.00 (7H, m,	

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40	253-253.5°C (dec) (EtOH)	3300, 2950, 2870, 2700, 1590, 1445, 1095, 1000, 740, 700	0.76 (3H, d, J = 6 Hz, CHCH <sub>3</sub> ) 0.77 (3H, d, J = 6 Hz, CHCH <sub>3</sub> ) 0.96-2.05 (11H, m,	<p>CH<sub>2</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>)<sub>2</sub>)</p> <p>2.24-2.93 (9H, m,</p> <p>CHNHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>)<sub>2</sub>)</p>
41	264.5-266.5°C (dec) (EtOH)	3280, 2940, 2870, 2670, 2590, 1590, 1435, 1255, 1110, 1095, 1050, 735 700	0.76 (3H, d, J = 6 Hz, CHCH <sub>3</sub> ) 0.78 (3H, d, J = 6 Hz, CHCH <sub>3</sub> ) 1.00-1.85 (7H, m,	<p>CH<sub>2</sub>CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>)<sub>2</sub>)</p> <p>2.24-2.88 (9H, m,</p> <p>CHNHCH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>)<sub>2</sub>)</p> <p>3.69 (4H, t, J = .5 Hz,</p> <p>CH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>)</p> <p>4.76 (1H, d, J = .4 Hz, CH-O)</p> <p>7.32(5H, m, aromatic protons)</p>

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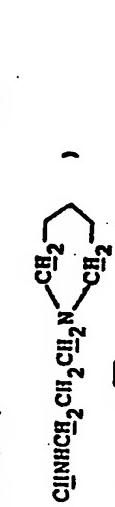
42	248-249°C (dec) (EtOH-c.HCl)	3310, 2950, 2680, 2510, 1590, 1465, 1445, 1110, 1050, 1030, 740, 700	0.75 (3H, d, J = 6 Hz, CHCH <sub>3</sub> ) 0.77 (3H, d, J = 6 Hz, CHCH <sub>3</sub> ) 0.96-1.90 (7H, m, CH <sub>2</sub> C <sub>11</sub> H <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub> , CH <sub>2</sub> CH <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub> ) 2.10-2.45 (2H, m, CH <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub> ) 2.21 (6H, s, N (CH <sub>3</sub> ) <sub>2</sub> ) 2.45-2.87 (3H, m, CHNHCH <sub>2</sub> ) 4.77 (1H, d, J = 4 Hz, CH-O) 7.29(5H, m, aromatic protons)	CH <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub> 2.21 (6H, s, N (CH <sub>3</sub> ) <sub>2</sub> ) 2.45-2.87 (3H, m, CHNHCH <sub>2</sub> ) 4.77 (1H, d, J = 4 Hz, CH-O) 7.29(5H, m, aromatic protons)
43	228-229°C (dec) (EtOH-c.HCl)	3320, 2960, 2870, 2680, 2600, 2480, 1580, 1445, 1350, 1095, 1020, 740, 700	0.76 (3H, d, J = 6 Hz, CHCH <sub>3</sub> ) 0.79 (3H, d, J = 6 Hz, CHCH <sub>3</sub> ) 0.98-1.58 (5H, m, CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub> ) 1.58-2.03 (4H, m, N CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> ) 2.27-2.98 (9H, m, CHNHCH <sub>2</sub> CH <sub>2</sub> N CH <sub>2</sub> CH <sub>2</sub> ) 4.74 (1H, d, J = 4 Hz, CH-O) 7.30 (5H, m, aromatic protons)	0.76 (3H, d, J = 6 Hz, CHCH <sub>3</sub> ) 0.79 (3H, d, J = 6 Hz, CHCH <sub>3</sub> ) 0.98-1.58 (5H, m, CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub> ) 1.58-2.03 (4H, m, N CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> ) 2.27-2.98 (9H, m, CHNHCH <sub>2</sub> CH <sub>2</sub> N CH <sub>2</sub> CH <sub>2</sub> ) 4.74 (1H, d, J = 4 Hz, CH-O) 7.30 (5H, m, aromatic protons)

44	242.5-244°C (dec) (EtOH)	3330, 2940, 2880, 2720, 1590, 1450, 1100, 1050, 740, 700  <chem>CCN(CCNC)CCN(CCNC)CC</chem>	0.75 (3H, d, J = 6 Hz, CHCH <sub>3</sub> ) 0.77 (3H, d, J = 6 Hz, CHCH <sub>3</sub> ) 0.95-1.03 (15H, m, CH <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub> , CH <sub>2</sub> CH <sub>2</sub> N CH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> ) 2.36-2.88 (9H, m, CHNHCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> N CH <sub>2</sub> CH <sub>2</sub> ) 4.77 (1H, d, J = 4 Hz, CH-O) 7.30 (5H, m, aromatic protons)
45	236-238°C (dec) (IsoproH-II <sub>2</sub> O)	3330, 2940, 2670, 2540, 1575, 1440, 1280, 1135, 1075, 1035, 950, 745  <chem>CCN(CCNC)c1ccccc1</chem>	0.64 (3H, d, J = 6 Hz, CHCH <sub>3</sub> ) 0.79 (3H, d, J = 6 Hz, CHCH <sub>3</sub> ) 0.86-1.00 (11H, m, CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub> , CH <sub>2</sub> CH <sub>2</sub> N CH <sub>2</sub> CH <sub>2</sub> ) 2.12-2.54 (6H, m, CH <sub>2</sub> N CH <sub>2</sub> CH <sub>2</sub> ) 2.29 (3H, s, - -) 2.54-3.04 (3H, m, CHNHCH <sub>2</sub> ) 5.05 (1H, d, J=3Hz, CH-O) 6.92-7.28, 7.40-7.64 (4H, m, aromatic protons)

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46	255-256°C (dec) (90% EtOH)	3280, 2930, 2680, 2540, 1600, 1440, 1075, 785, 755, 700	$\text{CH}_2\text{CH}(\text{CH}_3)_2$ , $\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)$ $\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)$	0.72 (3H, d, J = 6 Hz, $\text{CHCH}_3$ ) 0.82 (3H, d, J = 6 Hz, $\text{CHCH}_3$ ) 0.86-1.86 (11H, m, 2.08-2.56 (6H, m, 2.34 (3H, s, $-\text{CH}_2-$ ) 2.56-2.96 (3H, m, $\text{CH}_3\text{NHCH}_2$ ) 4.77 (1H, d, J=4Hz, $\text{CH}-\text{O}$ ) 6.84-7.34 (4H, m, aromatic protons)
47	240-243°C (dec) (EtOH)	3300, 2940, 2680, 2550, 1590, 1450, 1045, 780, 705	$\text{CH}_2\text{CH}(\text{CH}_3)_2$ , $\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)$ $\text{CH}_2\text{N}(\text{CH}_2\text{CH}_2)$	0.77 (3H, d, J = 7 Hz, $\text{CHCH}_3$ ) 0.85 (3H, d, J = 7 Hz, $\text{CHCH}_3$ ) 1.02-1.76 (11H, m, 2.00-2.84 (9H, m, 2.33 (3H, s, $-\text{CH}_2\text{CH}_3$ ) 4.19 (1H, d, J=7Hz, $\text{CH}-\text{O}$ ) 6.88-7.28 (4H, m, aromatic protons)

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48	257-259°C (dec) (EtOH-H <sub>2</sub> O)	3400, 3340, 2950, 2680, 1430, 1080, 850, 805, 760 0.72 (3H, d, J = 6 Hz, CHCH <sub>3</sub> ) 0.82 (3H, d, J = 6 Hz, CHCH <sub>3</sub> ) 0.88-1.84 (11H, m, 2.10-2.54 (6H, m,  2.32 (3H, s, -C(=O)-CH <sub>3</sub> ) 2.56-2.90 (3H, m, CHNHCH <sub>2</sub> ) 4.76 (1H, d, J=4Hz, CH-O) 6.92-7.32 (4H, m, aromatic protons)	0.76 (3H, d, J = 7 Hz, CHCH <sub>3</sub> ) 0.83 (3H, d, J = 7 Hz, CHCH <sub>3</sub> ) 1.02-1.84 (11H, m, 2.08-2.88 (9H, m,  2.31 (3H, s, -C(=O)-CH <sub>3</sub> ) 8.12 (2H, broad s, OH, NH) 4.19 (1H, d, J=7Hz, CH-O) 6.92-7.36 (4H, m, aromatic protons)
49	243-246°C (dec) (EtOH)	3420, 3300, 2940, 2860, 2740, 1605, 1570, 1445, 1045, 955, 810 795	

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50	<p>250-251°C (dec) (90% EtOH)</p> <p>3370, 2930, 2680, 2540, 1605, 1505, 1440, 1250, 1170, 1075, 1030, 605</p>	<p>0.73 (3H, d, J = 6 Hz, CHCH<sub>3</sub>) 0.83 (3H, d, J = 6 Hz, CHCH<sub>3</sub>) 0.86-1.84 (11H, m, CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)<sub>2</sub>&gt;CH<sub>2</sub>) 2.08-2.52 (6H, m, CH<sub>2</sub>N(CH<sub>2</sub>)<sub>2</sub>)</p>	<p>CH<sub>2</sub>N(CH<sub>2</sub>)<sub>2</sub>) 2.52-2.88 (3H, m, CHNRCH<sub>2</sub>) 3.79 (3H, s, -O-C<sub>6</sub>H<sub>4</sub>-) 4.74 (1H, d, J=4Hz, CH-O) 6.66-6.90, 7.02-7.32 (4H, m, aromatic protons)</p>
51	<p>275-276°C (dec) (EtOH-H<sub>2</sub>O)</p> <p>3400, 3260, 2960, 2680, 2530, 1605, 1505, 1465, 1450, 1430, 1390, 1370, 1285, 1230, 1160, 1140, 1080, 1040, 1010, 950, 830, 810, 785, 700</p>	<p>0.71 (3H, d, J = 6 Hz, CHCH<sub>3</sub>) 0.82 (3H, d, J = 6 Hz, CHCH<sub>3</sub>) 0.89-1.85 (11H, m, CH<sub>2</sub>CH(CH<sub>3</sub>)<sub>2</sub>, CH<sub>2</sub>CH<sub>2</sub>N(CH<sub>2</sub>)<sub>2</sub>&gt;CH<sub>2</sub>) 2.12-2.57 (6H, m, CH<sub>2</sub>N(CH<sub>2</sub>)<sub>2</sub>)</p>	<p>2.5-6.0 (2H, broad s, OH, NH) 2.57-2.92 (3H, m, CHNICH<sub>2</sub>) 4.77 (1H, d, J=3Hz, CH-O) 6.80-7.44 (4H, m, aromatic protons)</p>

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52	250-251°C (dec) (EtOH)	3300, 2940, 2870, 2640, 2550, 1605, 1585, 1450, 1230, 1155, 1050, 835 0.75 (3H, d, J = 6 Hz, CHCH <sub>3</sub> ) 0.85 (3H, d, J = 6 Hz, CHCH <sub>3</sub> ) 0.92-1.81 (11H, m, CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub> , CH <sub>2</sub> CH <sub>2</sub> N<sup>CH</sub> <sub>2</sub> >-CH <sub>2</sub> -CH <sub>2</sub> ) 2.10-2.86 (9H, m, CH <sub>2</sub> NHCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> N<sup>CH</sub> <sub>2</sub> >-CH <sub>2</sub> ) 4.20 (1H, d, J=7Hz, CH-O) 6.77-7.44 (4H, m, aromatic protons)	
53	278-279°C (dec) (EtOH-H <sub>2</sub> O)	3400, 3260, 2940, 2860, 2680, 2550, 1600, 1470, 1445, 1390, 1370, 1140, 1085, 1040, 1015, 960, 850, 800 0.71 (3H, d, J = 6 Hz, CHCH <sub>3</sub> ) 0.82 (3H, d, J = 6 Hz, CHCH <sub>3</sub> ) 0.84-1.84 (11H, m, CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub> , CH <sub>2</sub> CH <sub>2</sub> N<sup>CH</sub> <sub>2</sub> >-CH <sub>2</sub> ) 2.08-2.54 (6H, m, CH <sub>2</sub> N<sup>CH</sub> <sub>2</sub> >-CH <sub>2</sub> ) 2.54-2.91 (3H, m, CHNHCH <sub>2</sub> ) 4.77 (1H, d, J=4Hz, CH-O) 7.27 (4H, m, aromatic protons)	

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54	252-253°C (dec) (EtOH)	3400, 1580, 1200, 815, 3230, 1450, 1140, 800 2950, 1430, 1090, 1060, 1015, 2700, 1390, 1060, 1015, 2560, 1370, 1045, 845, 1600, 1370, 1045, 845, 0.76 (3H, d, J = 6 Hz, CH <sub>2</sub> CH <sub>3</sub> ) 0.85 (3H, d, J = 6 Hz, CH <sub>2</sub> CH <sub>3</sub> ) 0.95-1.77 (11H, m, CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub> , CH <sub>2</sub> CH <sub>2</sub> N(CH <sub>2</sub> ) <sub>2</sub> CH <sub>2</sub> ) 2.10-2.82 (9H, m, CH <sub>2</sub> NHCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> N(CH <sub>2</sub> ) <sub>2</sub> CH <sub>2</sub> ) 4.20 (1H, d, J=7Hz, CH <sub>2</sub> -O) 7.28 (4H, m, aromatic protons)
55	256-257°C (dec) (EtOH)	3300, 1445, 1090, 2930, 1400, 1065, 1010, 2860, 1350, 950, 2680, 1285, 1200, 1135, 2550, 1200, 700 1600, 1135, 0.68-0.98 (3H, m, CH <sub>2</sub> CH <sub>3</sub> ) 0.98-1.84 (22H, m, (CH <sub>2</sub> ) <sub>7</sub> CH <sub>3</sub> , CH <sub>2</sub> CH <sub>2</sub> N(CH <sub>2</sub> ) <sub>2</sub> CH <sub>2</sub> ) 2.12-2.53 (6H, m, CH <sub>2</sub> N(CH <sub>2</sub> ) <sub>2</sub> CH <sub>2</sub> ) 2.53-2.86 (3H, m, CH <sub>2</sub> NHCH <sub>2</sub> ) 4.77 (1H, d, J=4Hz, CH <sub>2</sub> -O) 7.29 (5H, m, aromatic protons)

Reference Example 12-(1,3-Dioxo-2-azaindan-2-yl)-4-methyl-1-  
phenylpentan-1-one

Thionyl chloride (34.8 ml, 480 mmol) was added to a  
5 mixture of 2-(1,3-dioxo-2-azaindan-2-yl)-4-methylpentanoic acid (83.61 g, 320 mmol) and benzene (320 ml). The resulting mixture was heated under reflux for 2 hours. The solvent and excess thionyl chloride were removed by distillation under reduced pressure, followed by addition  
10 of benzene (320 ml). The benzene was removed and fresh benzene (480 ml) was added to form a solution. Anhydrous aluminum chloride (106.7 g, 800 mmol) was added immediately to the solution and the mixture was stirred at room temperature for 3 hours. The reaction mixture was poured  
15 into ice-water (700 ml). The aqueous layer was extracted with benzene (200 ml). After being washed first with water and then with an aqueous sodium bicarbonate solution and with brine, the combined organic layer was dried over sodium sulfate and then evaporated under reduced pressure.  
20 The residue was treated with ethanol to give crystals. The crystals were dissolved with heating in ethanol (80 ml) and hexane (160 ml) was added. Precipitated crystals were collected by filtration and washed first with a 1:2 mixed solution (240 ml) of ethanol and hexane and then with  
25 hexane. The crystals were dried in air to obtain 74.6 g of the title compound as white crystals (yield: 73%).

Reference Example 2

(1RS,2SR)-2-(1,3-Dioxo-2-azaindan-2-yl)-4-methyl-  
1-phenylpentan-1-ol and (1RS,2RS)-2-(1,3-dioxo-  
2-azaindan-2-yl)-4-methyl-1-phenylpentan-1-ol

5      Sodium cyanoborohydride (177 g, 2.82 mol) was added over 3 hours to a solution of the compound (141.4 g, 440 mmol) obtained in Reference Example 1 in chloroform (660 ml) and acetic acid (440 ml) while maintaining the reaction temperature below 30°C. The resulting mixture was stirred 10 at room temperature for further 3 hours and then chloroform (1 liter) and water (1.4 liters) were added. The organic layer was separated and washed twice with water, once with an aqueous sodium bicarbonate solution and once with brine. After being dried over sodium sulfate, the organic layer 15 was evaporated under reduced pressure to provide white crystals (142 g). The crystals were then charged on silica gel column chromatography (silica gel: 2.8 kg, solvent: benzene) to obtain first 94.3 g of the (1RS,2SR) isomer as white crystals (yield: 66%) and then 48.4 g of the 20 (1RS,2RS) isomer as white crystals (yield: 34%).

Reference Example 3

(1RS,2RS)-2-(1,3-Dioxo-2-azaindan-2-yl)-4-  
methyl-1-phenylpentan-1-ol

Aluminum isopropoxide (125.6 g, 615 mmol) was added 25 to a suspension of 2-(1,3-dioxo-2-azaindan-2-yl)-4-methyl-1-phenylpentan-1-one (72.3 g, 225 mmol) in isopropanol

(1,000 ml). The mixture was heated under reflux for 6.5 hours. The isopropanol was removed by distillation under reduced pressure and to the residue were added ethyl acetate (800 ml) and an aqueous solution of sodium sulfate.

5 The resulting organic layer was decanted and the residue was washed twice with ethyl acetate (200 ml). The combined organic layer was washed with brine. The organic solution was dried and the solvent was removed by distillation under reduced pressure. The residue was recrystallized twice  
10 from benzene to obtain 29.3 g of the title compound as white crystals (yield: 40%).

Reference Example 4

(1RS,2SR)-2-Amino-4-methyl-1-phenylpentan-1-ol

(1RS,2SR)-2-(1,3-Dioxo-2-azaindan-2-yl)-4-methyl-1-phenylpentan-1-ol (80.0 g, 247 mmol) was dissolved with heating (50°C) in ethanol (800 ml), followed by addition of a mixture of 85% hydrazine hydrate (19.0 ml) in ethanol (200 ml). The resulting mixture was heated under reflux for 3 hours. After ice-cooling, 4N-HCl (700 ml) was added.  
20 The mixture was stirred at room temperature for 30 minutes. Insoluble matter was removed by filtration through celite and then washed with 4N-hydrochloric acid (140 ml). The washing was added to the filtrate and the solution was condensed under reduced pressure to remove the ethanol. A  
25 6N-NaOH solution (570 ml) was added with ice-cooling and the mixture was extracted three times with chloroform.  
After being dried

over sodium sulfate, the organic layer was evaporated to obtain 43.2 g of the title compound as white crystals (yield: 91%).

Reference Example 5

5       4-Methyl-1-(4-methylphenyl)-2-(1,3-dioxo-2-azaindan-2-yl)pentan-1-one  
2-Bromo-4-methyl-1-(4-methylphenyl)pentan-1-one (13.5  
g, 50 mmol) and potassium phthalimide (9.26 g, 50 mmol)  
were thoroughly mixed and heated at 160°C for 2 hours.  
10 After cooling, to the reaction mixture were added ethyl  
acetate (100 ml) and water (50 ml). The resulting organic  
layer was separated and washed with brine. The organic  
solution was then dried over sodium sulfate and evaporated  
under reduced pressure. The residue was crystallized by  
15 treatment with hexane and the crystals were recrystallized  
from hexane to obtain 12.2 g of the title compound as white  
crystals (yield: 73%).

Reference Example 6

(1RS,2SR)-2-Amino-1-phenylheptan-1-ol  
20       A mixture of potassium hydroxide (15 g) in water (150  
ml) and 2-(1,3-dioxo-2-azaindan-2-yl)-1-phenylheptanone  
(20.1 g, 60 mmol) was refluxed for 30 minutes. After being  
cooled, the mixture was acidified with 5% hydrochloric  
acid. Precipitated white curd was separated by decan-  
25 tation. To the curd was added 225 ml of 5% hydrochloric  
acid and the mixture was refluxed for 1 hour and then  
allowed to stand overnight at room temperature. The white

precipitate was removed by filtration and the filtrate was concentrated under reduced pressure. The remaining water was removed as an ethanol azeotrope. The residue was treated with hexane to give 14.5 g of 2-amino-1-5phenylheptan-1-one hydrochloride (yield : 100%). To a cooled solution of the aminoketone hydrochloride (13.1 g) in methanol (130 ml) was added sodium borohydride (1.53 g, 40 mmol) in limited amounts so as to maintain the reaction temperature below 15 °C. Thereafter, the mixture was 10stirred at room temperature for 1 hour and concentrated under reduced pressure. To the residue was added chloroform and water. The mixture was basified with 2N-NaOH and the organic layer was separated. The aqueous layer was extracted twice with chloroform and the combined 15organic layer was washed with brine, dried over anhydrous sodium sulfate and then evaporated under reduced pressure. The residual white solid was recrystallized from hexane to obtain 7.95 g of the title compound as white crystals (yield : 71%).

20

Reference Example 7(1RS,2RS)-2-Amino-1-phenylheptan-1-ol

Acetic anhydride (10 ml) was added to (1RS,2SR)-2-amino-1-phenylheptan-1-ol (4.15 g, 20 mmol) and the mixture was heated at 70°C for 10 minutes. After being 25 cooled, the reaction mixture was poured into water (100 ml) to which chloroform was added, followed by gradual addition of an aqueous sodium hydroxide solution. The solution thus

basified was extracted with chloroform and the extract was dried. The solvent was removed by distillation under reduced pressure to obtain a colorless oil. The oil was ice-cooled, followed by addition of thionyl chloride (20 ml). The mixture was stirred at room temperature for 20 minutes. Water (30 ml) was added in limited amounts with caution and the mixture was heated under reflux for 2 hours. The mixture was cooled and then water was added. Subsequent to washing of the mixture with ether, the resulting aqueous layer was separated and basified with an aqueous sodium hydroxide solution. The mixture was extracted three times with chloroform and dried. The organic solution was evaporated under reduced pressure to give white crystals. The crystals were recrystallized from hexane to obtain 2.73 g of the title compound as white crystals (yield : 66%).

Reference Example 8

(1RS,2SR)-2-Amino-1-(4-methoxyphenyl)-4-methyl-  
pentan-1-ol

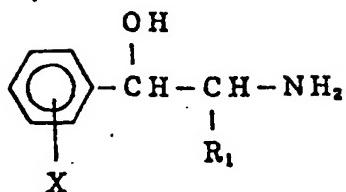
20        2-Hydroxyimino-1-(4-methoxyphenyl)-4-methylpentan-1-one (8.72 g, 37.1 mmol) was dissolved in acetic acid (88 ml). To the solution was added 5% palladium-charcoal (0.87 g) and the reactant was catalytically hydrogenated at normal pressure at 80°C until hydrogen was absorbed in a molar amount of three times that of the reactant. After removal of the catalyst by filtration, the acetic acid was removed under reduced pressure. The residue was dissolved

in 1N-HCl (80 ml). The solution was washed twice with ether (30 ml) and the aqueous layer was basified with a 20% aqueous solution of sodium hydroxide. The aqueous layer thus treated was extracted three times with chloroform and the extracts were combined together and then washed once with brine. The resulting extract was dried over sodium sulfate and the solvent was removed by distillation under reduced pressure to give light-yellowish crystals (6.80 g).

The crystals were recrystallized from benzene and hexane to obtain 5.24 g of the title compound as white crystals (yield : 63%).

Amino alcohols useful as the starting materials for the compounds of the invention were synthesized by the combined use of the methods illustrated in Reference Examples (Method A : Reference Examples 1, 2 and 4, Method B : Reference Examples 1 and 6, Method C : Reference Example 7, Method D : Reference Example 8, Method E : Reference Examples 5, 3 and 4, Method F : Reference Examples 5, 2 and 4). The melting points and synthetic methods of the starting materials thus obtained are given in Table 5.

Table 5



X	R <sub>1</sub>	Configura-tion	mp and/or [α] <sub>D</sub>	Synthetic method
H	-(CH <sub>2</sub> ) <sub>2</sub> CH <sub>3</sub>	1RS, 2SR	mp 66 - 66.5 °C	A
H	-(CH <sub>2</sub> ) <sub>2</sub> CH <sub>3</sub>	1RS, 2RS	mp 68.5 - 69 °C	A
H	-(CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub>	1RS, 2SR	mp 72.5 - 74 °C	A
H	-(CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub>	1RS, 2RS	mp 74 - 75 °C	A
H	-(CH <sub>2</sub> ) <sub>4</sub> CH <sub>3</sub>	1RS, 2SR	mp 67.5 - 68.5 °C	B
H	-(CH <sub>2</sub> ) <sub>4</sub> CH <sub>3</sub>	1RS, 2RS	mp 75 - 77 °C	C
H	-(CH <sub>2</sub> ) <sub>5</sub> CH <sub>3</sub>	1RS, 2SR	mp 79 - 80 °C	A
H	-(CH <sub>2</sub> ) <sub>5</sub> CH <sub>3</sub>	1RS, 2RS	mp 61 - 62 °C	A
H	-(CH <sub>2</sub> ) <sub>7</sub> CH <sub>3</sub>	1RS, 2SR	mp 77 - 78 °C	D
H		1RS, 2SR	mp 103 - 104.5 °C	A
H		1RS, 2RS	mp 60 - 62 °C	A
H		1RS, 2SR	mp 81 - 83 °C	A
H		1RS, 2RS	mp 72 - 73 °C	A
H		1R, 2S	mp 70 - 71 °C [α] <sub>D</sub> <sup>23</sup> -38.9° (cl.0, EtOH)	A

X	R <sub>1</sub>	Configura-tion	mp and/or [α] <sub>D</sub>	Synthetic method
H		1S, 2R	mp 70 - 71 °C [α] <sub>D</sub> <sup>23</sup> +39.0° (cl.0, EtOH)	A
H		1S, 2S	mp 65 - 66 °C [α] <sub>D</sub> <sup>23</sup> -10.3° (cl.0, EtOH)	A
H		1R, 2R	mp 65 - 66 °C [α] <sub>D</sub> <sup>23</sup> +10.3° (cl.0, EtOH)	A
H		1RS, 2SR	mp 92 - 93 °C	A
H		1RS, 2RS	mp 75 - 76 °C	A
2-CH <sub>3</sub>		1RS, 2SR	mp 64 - 65 °C	D
3-CH <sub>3</sub>		1RS, 2SR	mp 76 - 78 °C	D
3-CH <sub>3</sub>		1RS, 2RS	oil	C
4-CH <sub>3</sub>		1RS, 2SR	mp 75 - 76 °C	D
4-CH <sub>3</sub>		1RS, 2RS	mp 67.5 - 68.5 °C	E
4-OCH <sub>3</sub>		1RS, 2SR	mp 80 - 82 °C	D
4-F		1RS, 2SR	oil	D
4-F		1RS, 2RS	oil	E

X	R <sub>1</sub>	Configu- ration	mp and/or [α] <sub>D</sub>	Synthetic method
4-Cl	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	1RS, 2SR	mp 95 - 97 °C	F
4-Cl	-CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	1RS, 2RS	mp 68 - 71 °C	F

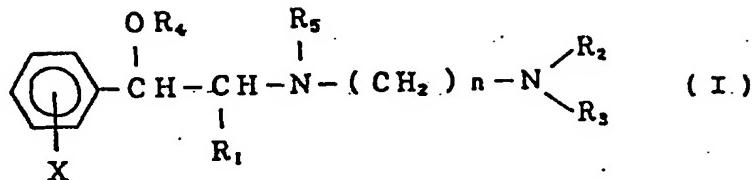
Reference Example 9

(4RS,5SR)-4-(3-Methylbutyl)-5-phenyl-3-(3-piperidinopropyl)-1,3-oxazolidin-2-one

A mixture of (4RS, 5SR)-4-(3-methylbutyl)-5-phenyl-5 1,3-oxazolidin-2-one [mp: 111-112 °C; prepared from (1RS,2SR)-2-amino-5-methyl-1-phenylhexan-1-ol by a known method {M. E. Dyen and D. Swern: Chem. Rev., 67, 197(1967)}] (1.17 g, 5 mmol), 1-(3-chloropropyl)piperidine hydrochloride (1.49 g, 7.5 mmol), anhydrous potassium 10 carbonate powder (2.07 g, 15 mmol) in methyl ethyl ketone (15 ml) was refluxed with stirring for 24 hours. After cooling, insoluble material was removed by filtration and washed with methyl ethyl ketone. The washing and filtrate were combined together and concentrated under 15 reduced pressure. The residue was purified by silica gel column chromatography (silica gel:35 g ; eluent: chloroform/methanol) to obtain 1.52 g of the title compound as an oil (yield : 85%).

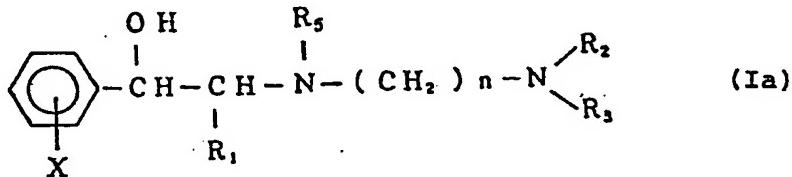
CLAIMS

1. An amino-alcohol derivative of the formula (I),



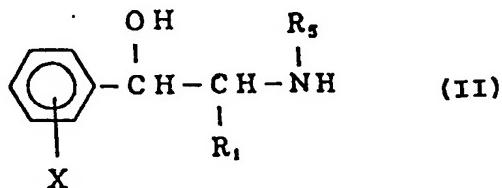
where  $R_1$  is a straight or branched alkyl group having 3 to 8 carbon atoms,  $R_2$  and  $R_3$  are each a lower alkyl group, or  $R_2$  and  $R_3$  form a 5- to 7-membered ring together with the adjacent nitrogen atom which may have an oxygen atom attached thereto,  $R_4$  is a hydrogen atom or a lower alkyl group,  $R_5$  is a hydrogen atom or a lower alkyl group,  $X$  is a hydrogen or halogen atom or a lower alkyl or lower alkoxy group, and  $n$  is an integer of 2 or 3, or an acid addition salt thereof.

2. A process for preparing an amino-alcohol derivative of the formula (Ia),

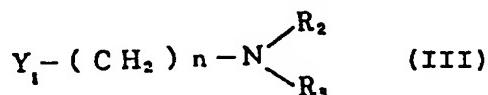


where  $R_1$  is a straight or branched alkyl group having 3 to 8 carbon atoms,  $R_2$  and  $R_3$  are each a lower alkyl group, or  $R_2$  and  $R_3$  form a 5- to 7-membered ring together with the adjacent nitrogen atom which may have an oxygen atom attached thereto,  $R_5$  is a hydrogen atom or a lower alkyl group,  $X$  is a hydrogen or halogen atom or a lower alkyl or

lower alkoxy group, and n is an integer of 2 or 3, or an acid addition salt thereof, which comprises reacting a compound of the formula (II),

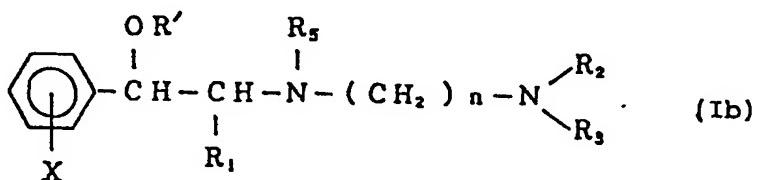


where  $\text{R}_1$ ,  $\text{R}_5$  and  $\text{X}$  are as defined above, with a compound of the formula (III),



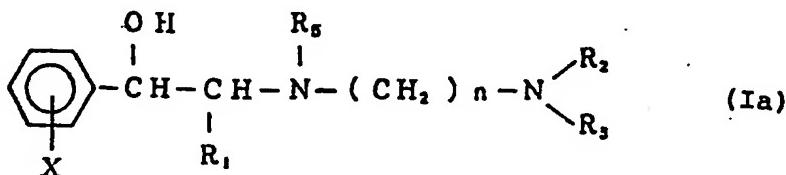
where  $\text{Y}_1$  is a halogen atom or a tosyloxy group, and  $\text{R}_2$ ,  $\text{R}_3$  and n are as defined above, and optionally converting the reaction product to an acid addition salt thereof.

### 3. A process for preparing an amino-alcohol derivative of the formula (Ib),

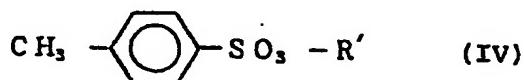


where  $\text{R}_1$  is a straight or branched alkyl group having 3 to 8 carbon atoms,  $\text{R}_2$  and  $\text{R}_3$  are each a lower alkyl group, or  $\text{R}_2$  and  $\text{R}_3$  form a 5- to 7-membered ring together with the adjacent nitrogen atom which may have an oxygen atom attached thereto,  $\text{R}_5$  is a hydrogen atom or a lower alkyl

group, R' is a lower alkyl group, X is a hydrogen or halogen atom or a lower alkyl or lower alkoxy group, and n is an integer of 2 or 3, or an acid addition salt thereof, which comprises reacting a compound of the formula (Ia),

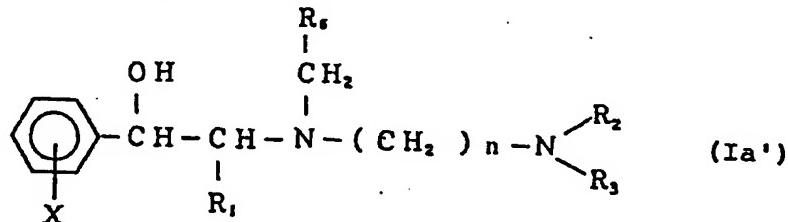


5 where R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>5</sub>, X and n are as defined above, with a compound of the formula (IV),



where R' is as defined above, and optionally converting the reaction product to an acid addition salt thereof.

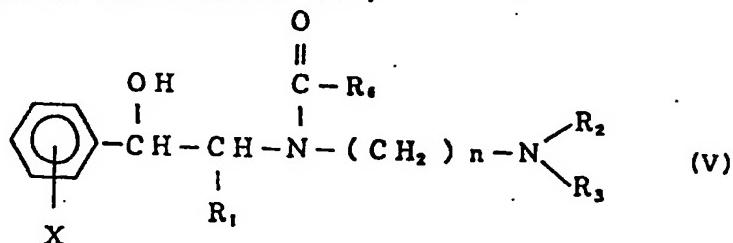
4. A process for preparing an amino-alcohol  
10derivative of the formula (Ia'),



where R<sub>1</sub> is a straight or branched alkyl group having 3 to 8 carbon atoms, R<sub>2</sub> and R<sub>3</sub> are each a lower alkyl group, or R<sub>2</sub> and R<sub>3</sub> form a 5- to 7-membered ring together with the adjacent nitrogen atom which may have an oxygen atom

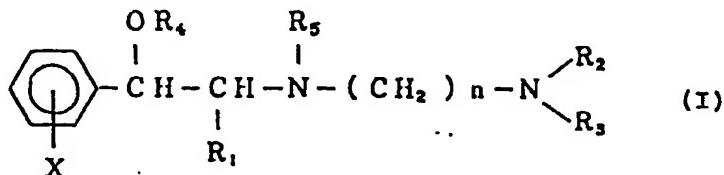
15 attached thereto, R<sub>6</sub> is a hydrogen atom or a lower alkyl

group, X is a hydrogen or halogen atom or a lower alkyl or lower alkoxy group, and n is an integer of 2 or 3, or an acid addition salt thereof, which comprises reducing a compound of the formula (V),

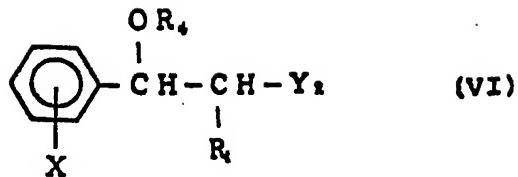


5 where  $\text{R}_1$ ,  $\text{R}_2$ ,  $\text{R}_3$ ,  $\text{R}_4$ , X and n are as defined above, and optionally converting the reaction product to an acid addition salt thereof.

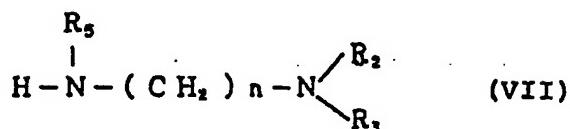
5. A process for preparing an amino-alcohol derivative of the formula (I),



10 where  $\text{R}_1$  is a straight or branched alkyl group having 3 to 8 carbon atoms,  $\text{R}_2$  and  $\text{R}_3$  are each a lower alkyl group, or  $\text{R}_2$  and  $\text{R}_3$  form a 5- to 7-membered ring together with the adjacent nitrogen atom which may have an oxygen atom attached thereto,  $\text{R}_4$  is a hydrogen atom or a lower alkyl group,  $\text{R}_5$  is a hydrogen atom or a lower alkyl group, X is a hydrogen or halogen atom or a lower alkyl or lower alkoxy group, and n is an integer of 2 or 3, or an acid addition salt thereof, which comprises reacting a compound of the formula (VI),

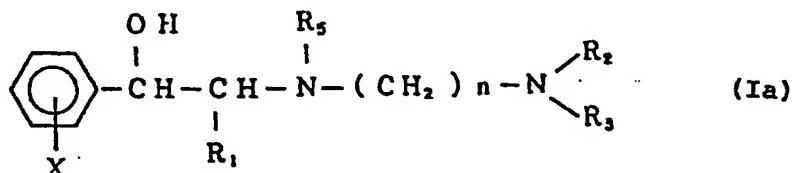


where  $Y_2$  is a halogen atom, and  $R_1$ ,  $R_4$  and  $X$  are as defined above, with a compound of the formula (VII),



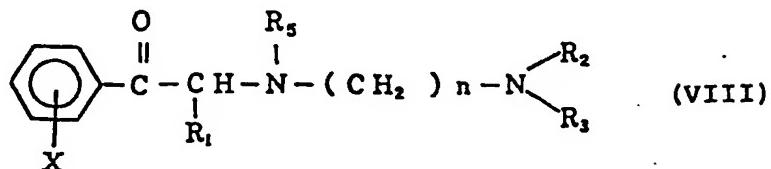
where  $R_2$ ,  $R_3$ ,  $R_5$  and  $n$  are as defined above, and optionally converting the reaction product to an acid addition salt thereof.

6. A process for preparing an amino-alcohol derivative of the formula (Ia),



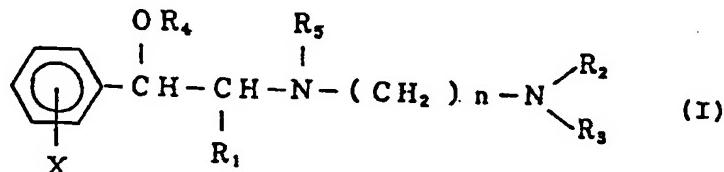
where  $R_1$  is a straight or branched alkyl group having 3 to 8 carbon atoms,  $R_2$  and  $R_3$  are each a lower alkyl group, or  $R_2$  and  $R_3$  form a 5- to 7-membered ring together with the adjacent nitrogen atom which may have an oxygen atom attached thereto,  $R_5$  is a hydrogen atom or a lower alkyl group,  $X$  is a hydrogen or halogen atom or a lower alkyl or lower alkoxy group, and  $n$  is an integer of 2 or 3, or an

acid addition salt thereof, which comprises reducing a compound of the formula (VIII),

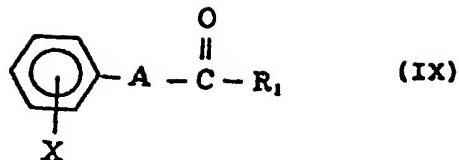


where  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_5$ ,  $X$  and  $n$  are as defined above, and optionally converting the reaction product to an acid addition salt thereof.

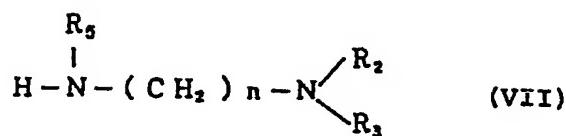
7. A process for preparing an amino-alcohol derivative of the formula (I),



where  $R_1$  is a straight or branched alkyl group having 3 to 8 carbon atoms,  $R_2$  and  $R_3$  are each a lower alkyl group, or  $R_2$  and  $R_3$  form a 5- to 7-membered ring together with the adjacent nitrogen atom which may have an oxygen atom attached thereto,  $R_4$  is a hydrogen atom or a lower alkyl group,  $R_5$  is a hydrogen atom or a lower alkyl group,  $X$  is a hydrogen or halogen atom or a lower alkyl or lower alkoxy group, and  $n$  is an integer of 2 or 3, or an acid addition salt thereof, which comprises reacting a compound of the formula (IX),

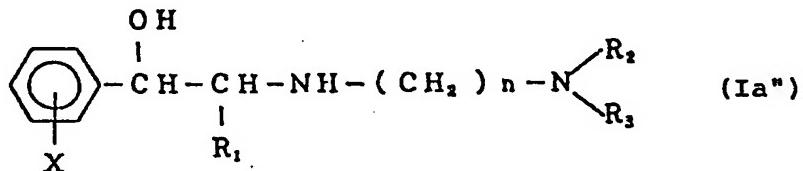


where A is  $\text{-C}=\text{}$  or  $\text{-CH-}$  in which  $R_4$  is as defined above, and  $R_1$  and X are as defined above, with a compound of the formula (VII),



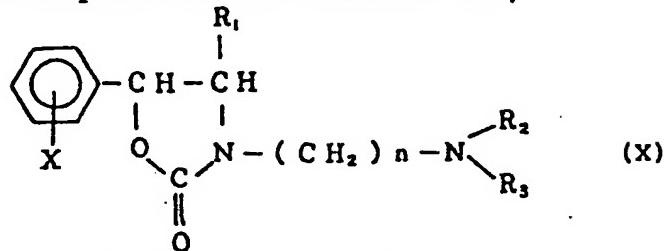
where  $R_2$ ,  $R_3$ ,  $R_5$  and  $n$  are as defined above, under reducing conditions, and optionally converting the reaction product to an acid addition salt thereof.

8. A process for preparing an amino-alcohol derivative of the formula (Ia''),



where  $R_1$  is a straight or branched alkyl group having 3 to 10 carbon atoms,  $R_2$  and  $R_3$  are each a lower alkyl group, or  $R_2$  and  $R_3$  form a 5- to 7-membered ring together with the adjacent nitrogen atom which may have an oxygen atom attached thereto, X is a hydrogen or halogen atom or a lower alkyl or lower alkoxy group, and  $n$  is an integer of 2

or 3, or an acid addition salt thereof, which comprises hydrolyzing a compound of the formula (X),



where  $R_1$ ,  $R_2$ ,  $R_3$ ,  $X$  and  $n$  are as defined above, and optionally converting the reaction product to an acid addition salt thereof.